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Research article

Rituximab-associated adverse events in nephrotic syndrome: A systematic review and meta-analysis

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ABSTRACT

Objective: Rituximab (RTX) has been recommended to treat nephrotic syndrome (NS), but its safety has not been quantitatively analyzed.

Methods: PubMed, Embase, and the Cochrane Register of Controlled Trials databases were searched from inception to December 31, 2023, for randomized control trials (RCTs) and retrospective studies reporting the adverse events (AEs) related to RTX for treating NS. Data were expressed as odds ratios (OR) and risk difference (RD) with 95 % confidence interval (CI). Heterogeneity was identified using the Cochrane Q test and quantified by the I^2 statistic.

Results: Ten RCTs and five retrospective studies with 1231 patients were enrolled. RTX significantly reduced the risk of total AEs (OR = 0.32, 95 % CI [0.13, 0.78]) compared to the non-RTX group in retrospective studies but was not in RCTs. The pooled rate of infusion reactions was 32 % (95 % CI = [19 %, 45 %]) in RCTs and 8 % (95 % CI = [3 %, 13 %]) in retrospective studies. Subgroup analyses demonstrated a lower risk of hematological events in adult NS patients (OR = 0.21, 95 % CI [0.09, 0.51]) and the 1000 mg RTX intervention (OR = 0.21, 95 % CI [0.09, 0.51]). There is no significant difference in serious AEs, infection, gastrointestinal, renal, cardiovascular, and cancer events between the two groups.

Conclusion: RTX reveals great potential in terms of safety compared to non-RTX treatments due to the relatively few AEs in our results. However, the interaction of other drugs needs to be monitored. The safety of RTX in NS patients needs to be further confirmed in high-quality clinical trials.

Abbreviations: Rituximab, RTX; Nephrotic syndrome, NS; randomized control trials, RCTs; adverse events, AEs; serious adverse events, SAEs; antibody-dependent cell-mediated cytotoxicity, ADCC; complement-dependent cytotoxicity, CDC; chronic kidney disease, CKD; end-stage renal disease, ESRD; membranous nephropathy, MN; Steroid-Dependent Nephrotic Syndrome, SDNS; focal segmental glomerulosclerosis, FSGS; minimal change disease, MCD; Mesangial proliferative glomerulonephritis, MsPGN; membranoproliferative glomerulonephritis, MPGN; estimated glomerular filtration rate, eGFR; non-Hodgkin's lymphoma, NHL; progressive multifocal leukoencephalopathy, PML; the Common Terminology Criteria for Adverse Events, CTCAE.

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1. Introduction

Nephrotic syndrome (NS) is one of the most prevalent kidney diseases accounting for approximately 3 per 100,000 person-years, which can cause severe and irreversible outcomes of chronic kidney disease (CKD) and even end-stage renal disease (ESRD) [1,2]. The pathogenesis of NS is a variety of pathological lesions of the kidney that result in increased permeability of the glomerular basement membrane, resulting in high-grade proteinuria, hypoproteinemia, hyperlipidemia, and edema. NS commonly happens in membranous nephropathy (MN), minimal change disease (MCD), focal segmental glomerular sclerosis (FSGS), mesangial proliferative glomerulonephritis (MsPGN), and membranoproliferative glomerulonephritis (MPGN) [3]. Research proved that B lymphocytes play an important role in the pathogenesis of NS [4,5]. Antibody production of B cells leads to the deposition of immune complexes in the glomerulus, and B cells, as antigen-presenting cells, can generate a variety of cytokines and inflammatory mediators to activate T cells, recognize innate immune cells, and result in kidney damage [6]. Numerous articles reporting the benefits of B-cell depletion therapy also support the contribution of B-cells in the pathogenesis of NS [7,8]. 27 % of MN patients achieved complete remission with a reduction of urinary protein excretion to the normal range and had fewer adverse events (AEs), but the lack of controls with immunosuppressive drugs or conservative therapy became the major limitation [9]. A retrospective study showed that MN patients in complete remissions were preceded by complete anti-phospholipase A2 receptor (anti-PLA2R) antibody depletion and 50 % anti-PLA2R titer reduction preceded equivalent proteinuria reduction by 10 months. However, the smaller sample sizes may affect the accuracy of the results [10]. In addition, due to the side effects of corticosteroids and immunosuppressants, it is imperative to explore new drugs that target B cell depletion in the treatment of NS.

Rituximab (RTX) is a monoclonal antibody against CD20-bearing cells that binds to CD20, depleting B lymphocytes through antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis pathways [11]. Numerous studies confirmed the efficacy of RTX in treating NS underlying diseases including MN, MCD, and so on [12,13]. However, there were no consistent results on AEs of RTX in NS patients. A recent meta-analysis only introduced one study to evaluate the incidence of infusion reactions of RTX in Steroid-Dependent Nephrotic Syndrome (SDNS) patients and found no significant difference between RTX and control group [14], while another meta-analysis reported the risk of infusion reactions in MN patients were higher in RTX group thanplacebo group [15]. In addition, some AEs reported by clinicians like anemia, diarrhea, and edema may influence the treatment effect of RTX, causing serious consequences to NS patients, which have not been analyzed previously [16,17]. Thus, more systematic and complete evidence is needed to evaluate the safety of RTX in NS patients.

Herein, we quantitatively evaluated RTX-related AEs including total AEs, serious adverse events (SAEs), infusion reactions, infection, hematological, gastrointestinal, renal, cardiovascular, and cancer events in NS patients, which have not been comprehensively analyzed before. Randomized controlled trials (RCTs) and retrospective studies are introduced and further analyzed separately to increase the credibility of the results.

2. Methods

This meta-analysis was registered in PROSPERO (CRD42022321414) beforehand and implemented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18] (Table S1).

2.1. Data Sources and search strategy

The PubMed, Embase, and Cochrane Register of Controlled Trials databases were searched from their inception to December 31, 2023. Mesh terms and free terms were used to retrieve all articles related to RTX and NS with language restricted to English. The literature search strategy included “nephrotic syndrome”, “idiopathic nephrotic syndrome”, “rituximab”, and “anti-CD20 monoclonal antibodies”. We additionally searched relevant meta-analysis and references to retrieve more comprehensive. Two reviewers (Zixian Yu and Meijin Huang) searched the title and abstract independently and then screened full texts to determine the eligibility of all literature. The controversies were resolved by discussion with the third author (Shiren Sun). Inclusion Criteria were as follows: (1) patients with clinically diagnosed nephrotic syndrome, (2) glomerular disease that often presents as nephrotic syndrome involving MN, FSGS, MCD, MsPGN, MPGN, (3) RCTs and retrospective studies reported the AEs after the administration of RTX, (4) patients in the RTX group received RTX treatment with or without other drugs. Exclusion Criteria were as follows: (1) single-arm studies, (2) the non-RTX group contained RTX, (3) patients with comorbidities like infectious disease or cancer, and (4) original studies with no available data.

2.2. Data extraction and bias assessment

Two authors (Zixian Yu and Jin Zhao) individually extracted data including basic characteristics (country, published year, median age, study design, number of patients, etc.), treatment, estimated glomerular filtration rate (eGFR), follow-up time, and AEs. The Cochrane risk of bias tool [19] was used to assess the quality of RCTs, and the Newcastle Ottawa quality assessment (NOS) scale [20] was employed to evaluate the quality of retrospective studies. If there exists any conflict, the third author (Shiren Sun) was consulted.

2.3. Statistical analysis

The infusion reactions ratio was pooled by risk difference (RD) with 95 % confidence interval (CI) using the inverse variance method and the dichotomous data were calculated by odds ratios (OR) with 95 % CI using the Mantel-Haenszel method. *P*-value <0.05 and 95 % CI not including one denotes that the difference was considered significant. According to the Cochrane Handbook, heterogeneity was assessed using the Cochrane Q test and I-square (I^2) statistics. High heterogeneity (I^2 ≥50 %) using the random effect model while the fixed effect model was used for low heterogeneity (I^2 < 50 %) [21]. Subgroup analysis was demonstrated based on different ages (below or above 18 years old), follow-up time (below or above 12 months), and initial doses of RTX (375 mg/m^2 or 1000 mg). Egger's test, Begg's test, and funnel plots were used to verify publication bias. The *P*-value <0.05 suggested publication bias. Review Manager 5.3 and Stata 14.0 were performed for statistical analysis.

3. Results

3.1. Study characteristics

We searched 5085 related studies from three databases. Ultimately, Fifteen studies including ten RCTs [12,16,17,22–28]and five retrospective studies [29–33]were identified after removing duplications, screening titles, abstracts, and full texts. The details of the search and screen are shown in Fig. 1 and Table S2. 1231 patients including 613 patients in the RTX group and 618 patients in the non-RTX group were enrolled. Patients in four RCTs were diagnosed with MN [12,16,22,25], and in six RCTs were diagnosed with SDNS or frequently relapsing nephrotic syndrome(FRNS) [23,24,27], multidrug-dependent nephrotic syndrome (DDNS) [8,17], and corticosteroid-dependent nephrotic syndrome (CDNS) [26]. Of the five retrospective studies, two studies included patients with MN [29,32] and three studies included patients with SDNS [30,31,33]. The treatment strategy in the RTX group included RTX alone, RTX plus steroids and calcineurin inhibitors (CNIs), RTX plus nonimmunosuppressive antiproteinuric treatment (NIAT), and in the non-RTX group, the treatment strategy embraced steroids plus CNIs, CNIs, ofatumumab, or placebo. The details of the study characteristics are listed in Table 1.

3.2. Risk of bias

In the RCTs, nine studies [8,12,16,17,22–25,27] were rated with a low risk of bias regarding the method of random sequence generation, and seven studies [8,12,16,22,23,25,26]were rated a high risk of bias in the blinding of participants and personnel performed because these studies were open-label studies. Six studies [8,16,22,23,25,26] reported the blinding of outcome assessment and rated with a high risk of bias, and a low risk of bias was reported in attrition and reporting bias (Fig. S1). The results of retrospective studies demonstrated that the score of all studies was 8 [29,30,32] and 7 [31,33] respectively, indicating the acceptable quality of all studies (Table S3). Egger's test and Begg's test showed that no publication bias was found except for total AEs and infusion reactions (Table S4). The funnel plots also showed no significant publication bias (Figure S2, Figure S3).

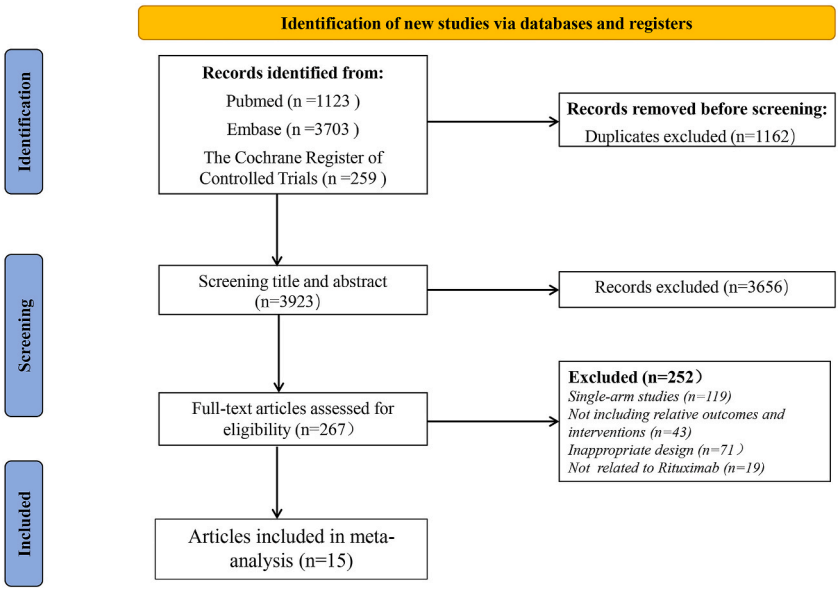

Fig. 1. Flow Diagram for searching, identifying, screening, and qualifying for all original studies.

Table 1
Basic characteristics of original studies.

Study	Disease	Country	RTX group	RTX dose	Non-RTX group	Study design	Sample Sizes (N)		eGFR (mL/min/1.73 m^2)	Proteinuria (g/24h)	Serum Albumin (g/L)	During (Month, M)	Age (Year, Y)	Adverse Events
							RTX group	Non-RTX group						
Fervenza, Fernando C et al. (2019)	MN	United States	RTX	1000 mg on days 1 and 15	CNIs	Multicenter, open-label RCT	65	65	RTX: 84.9 ± 29.8* Con: 87.4 ± 34.4	RTX:9.4 ± 4.16 Con:9.5 ± 4.70	RTX: 25 ± 6.1 Con: 25 ± 6.1	24 M	RTX:51.9 ± 12.6 Con:52.2 ± 12.4	Total AEs, SAEs, Infusion reactions, Infection events, GI events, CV events, Renal events
Scolari, Francesco et al. (2021)	MN	Italy	RTX	1000 mg on days 1 and 15	Steroids + CNIs	Multicenter, open-label RCT	37	37	RTX:83 ± 24 Con:86 ± 25	RTX:6.7 ± 4.6 Con:6.7 ± 3.1	RTX: 20 ± 10 Con: 20 ± 10	36 M	RTX:54 ± 14 Con:55 ± 17	Total AEs, SAEs, Infusion reactions, Infection events, Hematological events, CV events, Cancer events
Dahan, Karine et al. (2017)	MN	France	RTX + NIAT	375 mg/m^2, twice a week	NIAT	Multicenter RCT	37	38	RTX:68.3 ± 20.9 Con:73.2 ± 23.5	≥3.5	RTX: 21.6 ± 5.4 Con: 22.7 ± 4.6	17 M	RTX:53.0 ± 15.6 Con:58.5 ± 15.6	SAEs, Infection events, GI events, CV events, Renal events, Cancer events
Fernández-Juárez, Gema et al. (2021)	MN	Spain	Tacrolimus-rituximab	1000 mg	Corticosteroid-cyclophosphamide	Multicenter, open-label RCT	43	43	RTX:80.5 ± 21.6 Con:79.1 ± 25.5	RTX:8.6 ± 3.75 Con:7.9 ± 4.98	RTX: 24.9 ± 6.9 Con: 26 ± 4.6	24 M	RTX:55.2 ± 10.8 Con:56.2 ± 12.0	Total AEs, SAEs, Infusion reactions, Infection events, GI events, Hematological events, CV events, Renal events, Cancer events
Ahn, Yo Han et al. (2018)	DDNS	Korea	RTX + Steroids + CNIs	375 mg/m^2, once a week	Steroids + CNIs	Multicenter, open-label RCT	36	18	RTX:115.1 ± 32.7 Con:112.6 ± 35.9	–	–	12 M	RTX:13.5 ± 5.0 Con:12.5 ± 4.2	Total AEs, SAEs, Infusion reactions, Infection events
Mathew, Georgie et al. (2022)	FRNS or SDNS	India	RTX	375 mg/m^2, once a week	CNIs	Open-label RCT	20	20	RTX:137.9 ± 22.2 Con:138.8 ± 25.8	–	RTX: 37.9 ± 5.6 Con: 39.2 ± 7.2	12 M	RTX:9.1 ± 2.8 Con:10.0 ± 5.1	Total AEs, SAEs, Infusion reactions, Infection events, Hematological events, GI events, Renal events
Iijima, Kazumoto et al. (2014)	FRNS or SDNS	Japan	RTX	375 mg/m^2, once a week	Placebo	Multicenter double-blind, RCT	24	24	RTX:128.9 ± 20.6 Con:126.4 ± 26	–	RTX: 34 ± 6 Con: 34 ± 5	12 M	RTX:11.5 ± 3.7 Con:13.6 ± 2.2	Total AEs, SAEs, Infusion reactions, Infection events, Hematological events, GI events, CV events, Renal events

(*continued on next page*)

Table 1 (*continued*)

Study	Disease	Country	RTX group	RTX dose	Non-RTX group	Study design	Sample Sizes (N)		eGFR (mL/min/1.73 m^2)	Proteinuria (g/24h)	Serum Albumin (g/L)	During (Month, M)	Age (Year, Y)	Adverse Events
							RTX group	Non-RTX group						
Basu, Biswanath et al. (2018)	CDNS	India	RTX	375 mg/m^2, once a week	CNIs	Open-label, RCT	60	60	RTX:100.2 ± 8.6 Con:103.0 ± 10.8	–	RTX: 41.8 ± 7.3 Con: 43.4 ± 8.1	12 M	RTX:7.1 ± 2.8 Con:7.2 ± 2.8	Total AEs, Infusion reactions, Infection events
Ravani, Pietro et al. (2011)	DDNS	Italy	RTX + Steroids + CNIs	375 mg/m^2, once or twice a week	Steroids + CNIs	Open-label RCT	27	27	> 60	RTX:1.6 ± 3.4 Con:1.6 ± 2.1	RTX: 36 ± 9 Con: 32 ± 8	12 M	RTX:10.2 ± 4.0 Con:11.3 ± 4.3	Infusion reactions
Ravani, Pietro et al. (2021)	SDNS	Italy	RTX	375 mg/m^2, once a week	Ofatumumab	Open-label RCT	70	70	RTX:144 ± 34 Con:147 ± 31	RTX:0.08 ± 0.05 Con:0.09 ± 0.05	RTX: 40 ± 10 Con: 40 ± 10	24 M	RTX:10 ± 7.4 Con:11 ± 7.4	Total AEs, Infusion reactions, Hematological events
Van den Brand, J et al. (2017)	MN	Netherlands	RTX	375 mg/m^2, once a week	Steroids + CNIs	Retrospective observational cohort study	100	103	RTX:59.1 ± 26.6 Con:58.4 ± 22.8	> 3.5	RTX: 22.3 ± 6.8 Con: 21.6 ± 6.6	40 M	RTX:51.5 ± 15.9 Con:55.3 ± 12.7	Total AEs, SAEs, Cancer events
Zhu, Fan et al. (2021)	MN	China	RTX + CNIs	100 mg	CNIs	Retrospective cohort study	26	41	RTX:94.2 ± 24.7 Con:88.5 ± 19.8	RTX:2158.1 ± 2412.9 Con:3732.1 ± 3190.3	RTX: 25.1 ± 5.6 Con: 25.9 ± 5.9	12 M	RTX:41.7 ± 14.8 Con:44.3 ± 10.6	Total AEs, Infusion reactions, Infection events, CV events
Bonanni, Alice et al. (2018)	SDNS	Italy	RTX	375 mg/m^2	Ofatumumab	Retrospective study	30	37	–	–	≤25	At least 12 M	RTX:4.5 ± 3.5 Con:11.1 ± 5.9	Total AEs, Infection events, Infusion reactions, CV events
DaSilva I et al. (2017)	SDNS or FRNS	Spain	RTX + Steroids + immunosuppressant	At least 1000 mg	Steroids + immunosuppressant	Multicenter retrospective study	28	22	RTX:86 ± 21 Con:89 ± 27	RTX:7.1 ± 3.5 Con:9.8 ± 5.2	RTX: 19.7 ± 4.8 Con:19.3 ± 5.2	31 M	RTX:25 ± 19 Con:27 ± 22	Infusion reactions
Sinha, Aditi et al. (2012)	SDNS	India	RTX	375 mg/m^2, once a week	CNIs	Retrospective study	10	13	RTX: 102.6 ± 28.3 Con: 96.7 ± 25.8	–	RTX: 38 ± 5 Con: 31 ± 9	12 M	RTX:12.2 ± 2.3 Con:12.3 ± 3.0	Infusion reactions, Renal events

DDNS multidrug-dependent nephrotic syndrome, including steroid- and calcineurin- dependent nephrotic syndrome; SNDS steroid-dependent nephrotic syndrome; CDNS corticosteroid-dependent nephrotic syndrome; FRNS frequently relapsing nephrotic syndrome; MN membranous nephropathy; RTX rituximab; CNIs calcineurin inhibitors; NIAT nonimmunosuppressive antiproteinuric treatment; RCT randomized control trial; eGFR estimated glomerular filtration rate; AE adverse event; SAEs serious adverse events; GI gastrointestinal; CV cardiovascular.

* Creatinine clearance replace estimated glomerular filtration rate

Data are presented as mean ± standard deviation (SD) unless otherwise indicated

3.3. Meta-analysis results

3.3.1. Total adverse events

Seven RCTs [12,16,17,22,24,26,27] and three retrospective studies [29,30,32] assessed total AEs. Total AEs were defined as an untoward and unintended reaction related to any dose. Our results showed there was no significant difference in RCTs (OR = 0.87, 95 % CI [0.58, 1.32]) compared with RTX group and non-RTX group (Fig. 2a), but the RTX group had a lower incidence of total AEs compared to the non-RTX group in retrospective studies (OR = 0.32, 95 % CI [0.13, 0.78]) (Fig. 2b).

Subgroup analysis showed no significant difference relative to the incidence of total AEs between the RTX group and the non-RTX group with different ages (children: OR = 1.10, 95 % CI [0.60, 2.01]; adults: OR = 0.71, 95 % CI [0.40, 1.26]). Similar results were reproduced in subgroups with different follow-up times (≤12 months: OR = 0.95, 95 % CI [0.50, 1.80]; >12 months: OR = 0.83, 95 % CI [0.48, 1.42]) or with different initial RTX doses (375 mg/m^2: OR = 1.10, 95 % CI [0.60, 2.01]; 1000 mg: OR = 0.71, 95 % CI [0.40, 1.26]) (Table 2).

3.3.2. Serious adverse events

Seven RCTs [12,16,17,22–25] and one retrospective study [29] evaluated SAEs. Of which, four studies [12,16,22,29] defined SAEs as any untoward medical occurrence that results in death, life-threatening, requiring inpatient hospitalization, or causing prolongation of existing hospitalization, results in disability or permanent damage, or a congenital anomaly/birth defect in the offspring. Three studies [17,23,24] used the Common Terminology Criteria for Adverse Events (CTCAE) to assess SAEs, and one study [25] monitored SAEs by Unité de Recherche Clinique-Centre de Recherche Clinique de l'Est Parisien. Four studies [12,22,23,29] reported the incidence of SAEs in the RTX group was lower than that in the non-RTX group, and another four original studies [16,17,24,25] demonstrated the incidence of SAEs in the RTX group was higher than that in the non-RTX group. Two studies [16,29] reported death events in RTX group. The details of SAEs were launched in Table S5. There was no significant difference in the incidence of SAEs between the RTX group and the non-RTX group in RCTs (OR = 0.89, 95 % CI [0.56, 1.41]) (Fig. 2c). The retrospective study from van den Brand, Ruggenenti [29] found that nine patients occurred SAEs in 100 MN patients in the RTX group, and 30 of 103 patients happened in the non-RTX group (OR = 0.24, 95 % CI [0.11, 0.54]) (Fig. 2d).

Subgroup analysis showed no significant difference in the incidence of SAEs between the RTX group and the non-RTX group in different ages (children: OR = 1.55, 95 % CI [0.59, 4.10]; adults: OR = 0.75, 95 % CI [0.44, 1.28]), different follow-up times (≤12 months: OR = 1.55, 95 % CI [0.59, 4.10]; >12 months: OR = 0.75, 95 % CI [0.44, 1.28]) or different initial RTX doses (375 mg/m^2: OR = 1.45, 95 % CI [0.67, 3.14]; 1000 mg: OR = 0.67, 95 % CI [0.38, 1.21]) (Table 2).

3.3.3. Infusion reactions

Nine RCTs [8,12,16,17,22–24,26,27] and four retrospective studies [30–33] reported the incidence of infusion reactions. Among them, six studies [8,12,16,27,30,32] reported the infusion rate, and six studies [8,16,22,24,27,30] reported pretreatment strategies like methylprednisolone, cetirizine, and paracetamol to reduce the infusion rates. In the RTX group, the pooled incidence of infusion reactions was 32 % (95 % CI = [19 %, 45 %]) in RCTs (Fig. 3a), 8 % (95 % CI = [3 %, 13 %]) in retrospective studies (Fig. 3b).

Subgroup analysis connected with the incidence of infusion reactions in the RTX group showed that the incidence of infusion reactions in children and 375 mg/m^2 initial RTX treatment was 39 % (95 % CI = [18 %, 60 %]), and 19 % (95 % CI = [8 %, 30 %]) occurred in adults and 1000 mg initial RTX treatment. (Table 2).

3.3.4. Infection events

Seven RCTs [12,16,17,22,24–26] and two retrospective studies [30,32] evaluated infection events. Compared to the non-RTX group, the RTX group had no significant difference in reducing infection events in RCTs (OR = 0.83, 95 % CI [0.44, 1.56]) (Fig. 3c) and in retrospective studies (OR = 0.46, 95 % CI [0.15, 1.43]) (Fig. 3d).

The results from subgroup analysis showed there is no significant difference related to the incidence of infection events in children and adult patients (children: OR = 1.65, 95 % CI [0.25, 10.91]; adults: OR = 0.69, 95 % CI [0.42, 1.15]), different follow-up times (≤12

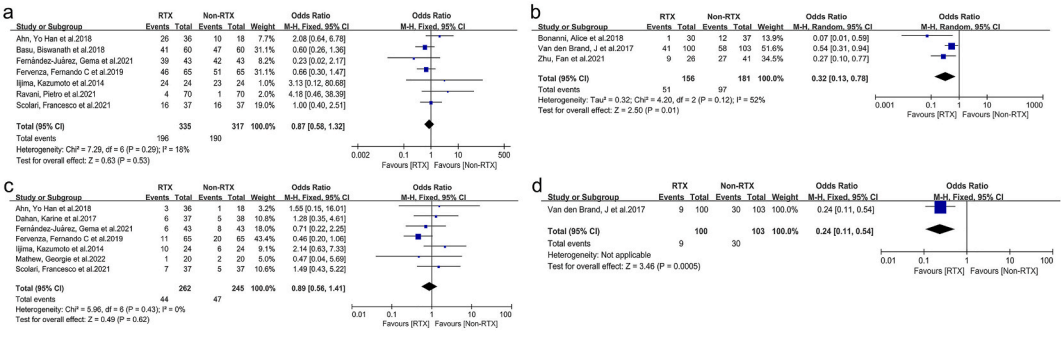

Fig. 2. Forest Plots of meta-analysis results. OR for total adverse events in patients with RTX vs. non-RTX group in RCTs (a) and retrospective studies (b), OR for serious adverse events in patients with RTX vs. non-RTX group in RCTs (c) and retrospective studies (d).

Table 2
Subgroup analysis of original studies in RCTs.

Outcome	Subgroup	Number	Odds Ratio (95 % CI)	*P*-value[a]	Heterogeneity(I^2)	Reference
Total adverse events	**Age**					
	Children	4	1.10 [0.60, 2.01]	0.76	40 %	[1–4]
	Adults	3	0.71 [0.40, 1.26]	0.25	0 %	[5–7]
	Follow-up					
	≤12 M	3	0.95 [0.50, 1.80]	0.87	42 %	[2–4]
	>12 M	4	0.83 [0.48, 1.42]	0.49	20 %	[1,5–7]
	RTX dose					
	375 mg/m^2	4	1.10 [0.60, 2.01]	0.76	40 %	[1–4]
	1000 mg	3	0.71 [0.40, 1.26]	0.25	0 %	[5–7]
Serious adverse events	**Age**					
	Children	3	1.55 [0.59, 4.10]	0.37	0 %	[2,3,8]
	Adults	4	0.75 [0.44, 1.28]	0.29	5 %	[5–7,9]
	Follow-up					
	≤12 M	3	1.55 [0.59, 4.10]	0.37	0 %	[2,3,8]
	>12 M	4	0.75 [0.44, 1.28]	0.29	5 %	[5–7,9]
	RTX dose					
	375 mg/m^2	4	1.45 [0.67, 3.14]	0.35	0 %	[2,3,8,9]
	1000 mg	3	0.67 [0.38, 1.21]	0.18	16 %	[5–7]
Infusion reactions	**Age**					
	Children	6	0.39 [0.18, 0.60]	<0.05	93 %	[1–4,8,10]
	Adults	3	0.19 [0.08, 0.30]	<0.05	68 %	[5–7]
	RTX dose					
	375 mg/m^2	6	0.39 [0.18, 0.60]	<0.05	93 %	[1–4,8,10]
	1000 mg	3	0.19 [0.08, 0.30]	<0.05	68 %	[5–7]
Infection events	**Age**					
	Children	3	1.65 [0.25, 10.91]	0.60	82 %	[2–4]
	Adults	4	0.69 [0.42, 1.15]	0.16	0 %	[5–7,9]
	Follow-up					
	≤12 M	3	1.65 [0.25, 10.91]	0.60	82 %	[2,3,9]
	>12 M	4	0.69 [0.42, 1.15]	0.16	0 %	[4–7]
	RTX dose					
	375 mg/m^2	4	1.47 [0.31, 6.92]	0.62	73 %	[2–4,9]
	1000 mg	3	0.68 [0.41, 1.15]	0.15	0 %	[5–7]
Hematological events	**Age**					
	Children	3	1.38 [0.55, 3.43]	0.49	0 %	[1,3,8]
	Adults	2	0.21 [0.09, 0.51]	<0.05	0 %	[6,7]
	Follow-up					
	≤12 M	2	1.14 [0.41, 3.15]	0.80	0 %	[3,8]
	>12 M	3	0.43 [0.07, 2.45]	0.34	57 %	[1,6,7]
	RTX dose					
	375 mg/m^2	3	1.38 [0.55, 3.43]	0.49	0 %	[1,3,8]
	1000 mg	2	0.21 [0.09, 0.51]	<0.05	0 %	[6,7]
Gastrointestinal events	**Age**					
	Children	2	0.34 [0.00, 68.62]	0.69	89 %	[3,8]
	Adults	3	0.89 [0.08, 9.91]	0.93	87 %	[5,7,9]
	Follow-up					
	≤12 M	2	0.34 [0.00, 68.62]	0.69	89 %	[3,8]
	>12 M	3	0.89 [0.08, 9.91]	0.93	87 %	[5,7,9]
	RTX dose					
	375 mg/m2	3	0.65 [0.01, 28.47]	0.83	83 %	[3,8,9]
	1000 mg	2	0.60 [0.03, 12.25]	0.74	93 %	[5,7]
Renal events	**Age**					
	Children	2	1.00 [0.35, 2.88]	1.00	83 %	[3,8]
	Adults	3	0.72 [0.14, 3.81]	0.70	29 %	[5,7,9]
	Follow-up					
	≤12 M	2	1.00 [0.35, 2.88]	1.00	83 %	[3,8]
	>12 M	3	0.72 [0.14, 3.81]	0.70	29 %	[5,7,9]
	RTX dose					
	375 mg/m^2	3	0.89 [0.34, 2.34]	0.81	0 %	[3,8,9]
	1000 mg	2	0.80 [0.10, 6.62]	0.84	92 %	[5,7]
Cardiovascular events	**Age**					
	Children	1	3.13 [0.12, 80.68]	0.49	–	[3]
	Adults	4	0.51 [0.24, 1.06]	0.07	6 %	[5–7,9]
	Follow-up					
	≤12 M	1	3.13 [0.12, 80.68]	0.49	–	[3]
	>12 M	4	0.51 [0.24, 1.06]	0.07	6 %	[5–7,9]
	RTX dose					
	375 mg/m^2	2	1.45 [0.27, 7.65]	0.66	0 %	[3,9]

(*continued on next page*)

Table 2 (*continued*)

Outcome	Subgroup	Number	Odds Ratio (95 % CI)	*P*-value[a]	Heterogeneity(I^2)	Reference
Cancer events	1000 mg	3	0.45 [0.20, 1.01]	0.15	28 %	[5–7]
	Age					
	Children	0				[6,7,9]
	Adults	3	0.78 [0.19, 3.21]	0.73	0 %	
	Follow-up					
	≤12 M	0				[6,7,9]
	>12 M	3	0.78 [0.19, 3.21]	0.73	0 %	
	RTX dose					[9]
	375 mg/m^2	1	0.33 [0.01, 8.45]	0.51	–	[6,7]
	1000 mg	2	1.00 [0.20, 5.09]	1.00	0 %	

RTX rituximab; ***M*** month.
a P < 0.05 indicates two groups have statistical significance.

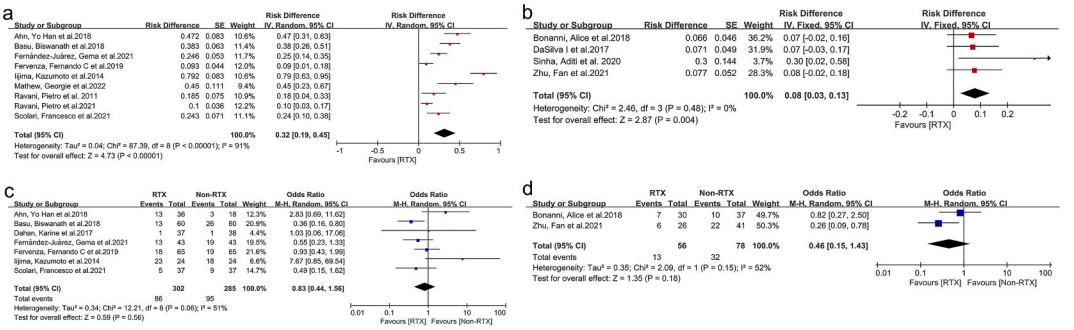

Fig. 3. Forest Plots of meta-analysis results. RD for infusion reaction rate of rituximab in RCTs (a) and retrospective studies (b), OR for infection events in patients with RTX vs. non-RTX group in RCTs (c) and retrospective studies (d).

months: OR = 1.65, 95 % CI [0.25, 10.91]; >12 months: OR = 0.69, 95 % CI [0.42, 1.15]), or different initial RTX doses (375 mg/m^2: OR = 1.47, 95 % CI [0.31, 6.92]; 1000 mg: OR = 0.68, 95 % CI [0.41, 1.15]) between the RTX group and the non-RTX group (Table 2).

3.3.5. Hematological events

Five RCTs [12,16,23,24,27] reported the relevant hematological events including anemia, leukocytopenia, lymphocytopenia, and neutropenia. The results showed that there was no significant difference between the two groups (OR = 0.65, 95 % CI [0.22, 1.93]) (Fig. 4a).

In the subgroup analysis, RTX significantly decreased the hematological events in adults (adults: OR = 0.21, 95 % CI [0.09, 0.51]) and 1000 mg RTX initial treatment (OR = 0.21, 95 % CI [0.09, 0.51]) compared to the non-RTX group. However, no significant difference was found in children (OR = 1.38, 95 % CI [0.55, 3.43]), 375 mg/m^2 RTX initial treatment (OR = 1.38, 95 % CI [0.55, 3.43]) and follow-up time (≤12 months: OR = 1.14, 95 % CI [0.41, 3.15]; >12 months: OR = 0.43, 95 % CI [0.07, 2.45]) between the RTX group and the non-RTX group (Table 2).

3.3.6. Gastrointestinal and renal events

Five RCTs [12,22–25] reported gastrointestinal and renal events and one retrospective study [33] reported renal events.

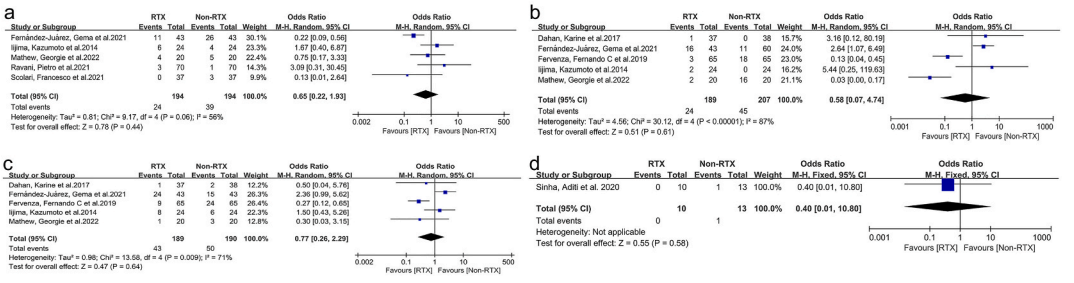

Fig. 4. Forest Plots of meta-analysis results. OR for hematological events in patients with RTX vs. non-RTX group in RCTs (a), OR for gastrointestinal events in patients with RTX vs. non-RTX group in RCTs (b), OR for renal events in patients with RTX vs. non-RTX group in RCTs (c) and retrospective studies (d).

Gastrointestinal events included diarrhea, abdominal complaints, gastritis, hepatitis, gastrointestinal pain, nausea, and vomiting. Renal events included acute kidney injury, edema, hyperkalemia, increased creatinine level, hemorrhagic cystitis, hyperuricemia, and hypoproteinemia. There were no significant differences in gastrointestinal events (OR = 0.58, 95 % CI [0.07, 4.74]) (Fig. 4b) and renal events (OR = 0.77, 95 % CI [0.26, 2.29]) in RCTs (Fig. 4c). The retrospective study reported that reversible nephrotoxicity occurred in the non-RTX group and no renal events were found in the RTX group (OR = 0.40, 95 % CI [0.01, 10.80]) (Fig. 4d).

Subgroup analysis related to the incidence of gastrointestinal events showed no significant difference in different ages (children: OR = 0.34, 95 % CI [0.00, 68.62]; adults: OR = 0.89, 95 % CI [0.08, 9.91]), different follow-up times (≤12 months: OR = 0.34, 95 % CI [0.00, 68.62]; >12 months: OR = 0.89, 95 % CI [0.08, 9.91]), and different initial RTX treatment (375 mg/m^2: OR = 0.65, 95 % CI [0.01, 28.47]; 1000 mg: OR = 0.60, 95 % CI [0.03, 12.25]) between the RTX group and the non-RTX group. No significant difference related to the incidence of renal events in different ages (children: OR = 1.00, 95 % CI [0.35, 2.88]; adults: OR = 0.72, 95 % CI [0.14, 3.81]), different follow-up times (≤12 months: OR = 1.00, 95 % CI [0.35, 2.88]; >12 months: OR = 0.72, 95 % CI [0.14, 3.81]), and different initial RTX treatments (375 mg/m^2: OR = 0.89, 95 % CI [0.34, 2.34]; 1000 mg: OR = 0.80, 95 % CI [0.10, 6.62]) (Table 2).

3.3.7. Cardiovascular events

Five RCTs [12,16,22,24,25] and two retrospective studies [30,32] declared cardiovascular events including hypertension, acute coronary syndrome, hypotension, stroke, myocardial infarction, critical limb ischemia, mesenteric ischemia, carotid endarterectomy, and aortoiliac femoral bypass. The results showed no significant difference between the RTX group and the non-RTX group in RCTs (OR = 0.57, 95 % CI [0.28, 1.15]) (Fig. 5a) and retrospective studies (OR = 0.64, 95 % CI [0.02, 18.88]) (Fig. 5b).

In subgroup analysis, no significant difference was found in adults (OR = 0.51, 95 % CI [0.24, 1.06]), follow-up times >12 months (OR = 0.51, 95 % CI [0.24, 1.06]), and different initial RTX doses (375 mg/m^2: OR = 1.45, 95 % CI [0.27, 7.65]; 1000 mg: OR = 0.45, 95 % CI [0.20, 1.01]) (Table 2).

3.3.8. Cancer events

Three RCTs [16,22,25] and one retrospective study [29] reported the incidence of cancer events, involving gastric adenocarcinoma, breast carcinoma, rectal carcinoma, lung cancer, and prostate cancer. There was no significant difference between the two groups (OR = 0.78, 95 % CI [0.19, 3.21) in RCTs (Fig. 5c). The result of van den Brand, Ruggenenti [29] reported three patients suffered cancer in the RTX group and eight patients suffered cancer in the non-RTX group (OR = 0.37, 95 % CI [0.09, 1.43]) (Fig. 5d).

No significant difference was found in adult patients (OR = 0.78, 95 % CI [0.19, 3.21]), follow-up time over 12 months (OR = 0.78, 95 % CI [0.19, 3.21]), and 1000 mg RTX treatment (OR = 1.00, 95 % CI [0.20, 5.09]) (Table 2).

3.3.9. Adverse events in membranous nephropathy

We further investigated the AEs in MN patients because of included studies were the largest and the important role of RTX in MN. Our results indicated that hematological events were reduced in the RTX group significantly compared to the non-RTX group in MN patients (OR = 0.65, 95 % CI [0.22, 1.93]). The rate of infusion events in MN patients was 19 %, lower than all NS patients. However, no significant differences were found in TAEs, SAEs, infection, gastrointestinal, renal, cardiovascular, and cancer events (Table 3).

4. Discussion

This meta-analysis evaluated AEs, including total AEs, SAEs, infusion reactions, infection, hematological, gastrointestinal, renal, cardiovascular, and cancer events associated with RTX in NS patients. RTX was associated with a lower risk of total AEs in NS patients in retrospective studies compared to the non-RTX group. The incidence of infusion reactions in NS patients was 32 % in RCTs and 8 % in retrospective studies. The subgroup analysis related to infusion reactions in RCTs demonstrated that the pooled rate of infusion reactions was 39 % in children NS patients, 19 % in adult patients, 39 % in 375 mg/m^2 RTX intervention, and 19 % in 1000 mg RTX intervention. The risk of hematological events was lower in the RTX group in pediatric patients, MN patient and 1000 mg initial RTX therapy compared to the non-RTX group. However, there were no significant differences in SAEs, infection, gastrointestinal, renal, cardiovascular, and cancer events. These results demonstrated the preferable tolerability and moderate side effects of RTX.

In nearly all of the original studies, total AEs were reported and were considered generally mild, demonstrating the potential safety

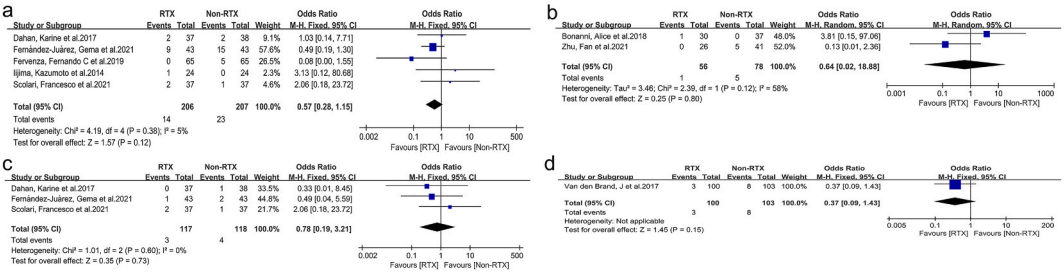

Fig. 5. Forest Plots of meta-analysis results. OR for cardiovascular events in patients with RTX vs. non-RTX group in RCTs (a) and retrospective studies (b), OR for cancer events in patients with RTX vs. non-RTX group in RCTs (c) and retrospective studies (d).

Table 3
Adverse events of Rituximab in membranous nephropathy in RCTs.

AEs	Study Number	Odds Ratio (95 % CI)	*P*-value[a]	Heterogeneity(I^2)
Total adverse events	3	0.71 [0.40, 1.26]	0.25	0 %
Serious adverse events	4	0.75 [0.44, 1.28]	0.29	5 %
Infusion events	3	0.19 [0.08, 0.30]	<0.05[a]	68 %
Infection events	4	0.69 [0.42, 1.15]	0.16	0 %
Hematological events	2	0.21 [0.09, 0.51]	<0.05[a]	0 %
Gastrointestinal events	3	0.89 [0.08, 9.91]	0.93	87 %
Renal events	3	0.72 [0.14, 3.81]	0.70	29 %
Cardiovascular events	3	0.78 [0.19, 3.21]	0.73	0 %
Cancer events	3	0.78 [0.19, 3.21]	0.73	0 %

a P < 0.05 indicates two groups have statistical significance.

of RTX in NS patients. The reduction in the risk of total AEs in the RTX group compared to the non-RTX group was found in retrospective studies rather than RCTs. This difference may be due to the fact that retrospective studies have the advantage over RCTs of having longer follow-up times, larger sample sizes, and known clinical outcomes such as observed safety. In addition, confounding factors may be another reason for the difference, because in RCTs, strict randomization and control design can minimize the interference of confounding factors, while retrospective studies cannot fully control or adjust all potential confounding variables. Chang, Gong [34] introduced three RCTs to evaluate total AEs in childhood refractory NS and found no significant difference between the RTX group and the control group, which coincided with ours. AEs were defined as an untoward and unintended response to a medicinal product related to any dose administered and SAEs included some severe conditions like death, life-threatening, required inpatient hospitalization, and so on [22]. Although the incidence of SAEs in our study involved various organs like benign neoplasms, cardiovascular, and endocrine systems, and had complex clinical symptoms like peritonitis, urticaria, and epigastric pain, SAEs after rituximab exposure are rare and no significant difference is found between the RTX group and the non-RTX group, which coincided with the results of Ou, Chen [35], and Hansrivijit, Cheungpasitporn [36]. A study reported that eleven SAEs in the RTX group are unrelated to treatment, whereas 38 of the 46 SAEs using steroid plus cyclical cyclophosphamide were considered possibly treatment-related, indicating RTX is probably more secure on SAEs than immunosuppressive therapy [29]. Researchers reported progressive multifocal leukoencephalopathy (PML), pulmonary fibrosis, and cancers may develop as late SAEs in RTX treatment, which did not occur during the period of observation and needed longer-term observation [17,37]. The mechanism of RTX-related SAEs is primarily associated with immune factors. For example, RTX causes prolonged depletion of B lymphocytes, which may lead to John Cunningham viral infection, resulting in PML [38]. Long-lasting immunosuppressant therapy patients may experience severe pulmonary infection even pulmonary fibrosis after RTX treatment [39]. These results reflect that early identification and continued monitoring of relevant symptoms and signs may facilitate intervention for AEs, such as rapid initiation of steroids and withdrawal [40].

The infusion reaction always occurs at the first infusion and is manifested by chills, fever, pruritus, rash, fatigue, etc. Infusion reactions related to RTX treatment frequently occurred but were reported as moderate in numerous diseases including rheumatoid arthritis, chronic lymphocytic leukemia, and kidney disease [41,42]. The pathogenesis may originate from IgE-mediated hypersensitivity or the release of cytokines such as Interleukin (IL)-1, IL-6, and Tumor Necrosis Factor (TNF)- α [43,44]. Reducing the infusion rate or using antihistamine and glucocorticoid therapy has been proven to improve anaphylactic reactions effectively [44]. It is noteworthy that a B-cell-driven protocol is equally effective but safer than the standard four 375 mg/m^2 doses of RTX [45]. Given that most of the non-RTX group received oral drugs, we conducted a single-arm analysis of the infusion reactions. According to previous studies, the pooled rates of RTX-related infusion reactions ranged from 26 % to 85 % [46]. The incidence approximately was 28 % in NS patients [47], and Fervenza, Appel [12]reported that 34 % of MN patients experienced infusion reactions, which showed the incidence of infusion reactions is similar to our results. Subgroup analysis revealed that for both children and adults, initial doses of 375 mg/m^2 and 1000 mg of RTX all influenced the incidence of infusion reactions, which may provide a basis for personalized administration of RTX in future clinical practice.

There was no significant difference in infection events in our study. A retrospective study reported an overall RTX-related infection rate of 4.5 % in idiopathic childhood NS patients with repeated RTX treatment, considered one of the most common AEs [48]. Low levels of B-cells, and IgG4, an important serum immunoglobulin, for protective immunity cause the dysfunction of $CD4^+$ T cells, which may be explained by an increased risk of infection after RTX treatment [49]. A meta-analysis found no significant difference in infection events after RTX treatment in NS patients, in line with our results [14]. However, immune-related factors like the combination of immunosuppressive treatment and hypogammaglobulinemia may cause pneumonia, skin infection, acute pyelonephritis, etc., leading to serious infection complications after RTX intervention [50]. The risk of infection associated with RTX should be considered and focused on prophylaxis like virus screening and vaccination.

Hematological events including anemia, leukocytopenia, lymphocytopenia, and neutropenia were specifically reported in our meta-analysis, which showed no significant difference between the RTX group and the non-RTX group. RTX group occurred lower hematological events compared with the non-RTX group in MN patients and subgroup analyses related to hematological events at different ages and initial RTX doses demonstrated a lower risk of hematological events in adult patients and the 1000 mg RTX intervention compared to the non-RTX group. The main treatment for MN patients is steroids combined with alkylating agents which have obvious hematological side effects and a high recurrence rate [51,52]. Increasing clinical trials like the MENTOR study [12] demonstrated RTX is an effective and safe drug in treating MN which is further confirmed by our results. The major treatment of RTX in

NS includes 375 mg/m^2 once per week for 4 weeks and 1000 mg per day on day 1 and day 15 [5]and our results showed that 1000 mg RTX intervention reduced the risk of hematological events. Although the mechanism of RTX in causing hematological events is unclear, researchers considered that the hematopoietic cells react communally with the rituximab antigen compound, leading to bone marrow suppression, which in turn causes a decline in granulocytes [53]. It has been reported that hematological events are usually asymptomatic and spontaneously recover, and granulocyte colony-stimulating factors should be used when leukocytopenia is considered to be associated with infection [47].

In order to comprehensively evaluate RTX-related AEs, we analyzed the risk of gastrointestinal, renal, cardiovascular, and cancer events that had not been completely reported before. However, no statistical difference was found in the above AEs when compared to the RTX group and non-RTX group. Subgroup analysis also showed similar results. Researchers indicated that immune and inflammation factors played an important role in the occurrence of these AEs [40,54,55]. RTX-associated gastrointestinal events like diarrhea and gastritis occurred more frequently in our study. RTX-associated colitis occurred in 4 % of patients who received a colonoscopy [56]. One potential mechanism of gastrointestinal events is the depletion of B cells induced regulatory T cell dysfunction resulting in mucosal damage [57]. Supplementing probiotics like *Lactobacillus reuteri* may alleviate RTX-related gastrointestinal symptoms [58]. As to renal events, Abbas, Mirza [55] reported acute kidney failure occurred in cancer patients who used RTX treatment. The incidence is most likely due to acute tumor lysis syndrome, and there is no direct relationship between RTX and kidney disease, suggesting that renal events may originate from the disease itself. Edema or hyperkalemia also happened in NS patients who used RTX. These renal events may be due to direct toxic effects on the kidney or secondary to tumor lysis syndrome [59,60]. Regarding cardiovascular events, Liu, Gui [14] found no significant difference in cardiovascular events, in line with us. An increased risk of hypotension and cardiac dysrhythmia happened in older age or patients who had underlying cardiac or pulmonary disease after the RTX treatment [61]. Therefore, early administration and prevention of blood pressure before RTX intervention is significant. Cancer events occurred less in our meta-analysis, in accordance with a 9.5-year follow-up clinical trial that considered no direct evidence of an increased cancer risk associated with RTX [62]. Six patients in the RTX group developed rectal carcinoma, lung cancer, breast cancer, or solid cancer, compared to 12 patients in the non-RTX group who developed gastric adenocarcinoma, breast cancer, prostate cancer, blood cancer, or solid cancer, indicating that cancer events occurred less often after RTX treatment. Some studies reported that the occurrence of cancer is not associated with the RTX injection [16,29]. van den Brand, Ruggenenti [29]considered patients who had cancer events treated by steroid plus cyclical cyclophosphamide likely related to treatment due to the carcinogenic effect of alkylating agents. However, patients with cancer events treated with RTX did not have an increased risk of cancer, which coincided with a large cohort study of rheumatic arthritis (RA) patients. The results prompted suggestions that RTX might be more secure against cancer than immunosuppressants. Although we detected some organic related AEs, other rare AEs like septic arthritis [63] not reported in this study need continuous attention.

4.1. Strengthen

This meta-analysis systematically verified the safety advantage of RTX in the treatment of NS. RTX demonstrated good safety, significantly reducing the risk of adverse reactions compared to non-RTX treatments, although infusion reactions required close monitoring. This finding aids primary care physicians in considering RTX as a relatively safe option when evaluating treatment options. Subgroup analysis revealed that adult patients receiving RTX at a dose of 1000 mg had a lower risk of hematological events, providing a valuable reference for physicians in formulating personalized treatment plans. Furthermore, this study comprehensively reviewed the potential systemic adverse reactions caused by RTX, providing comprehensive guidance for clinicians in complex situations and facilitating the optimization of treatment plans.

4.2. Limitation

This meta-analysis also had some limitations. First, only five retrospective studies were enrolled in this study which makes it impossible to perform subgroup analysis on different ages, follow-up times, and initial doses of RTX therapy, and the number of subgroups was small which may create statistical bias. Second, the treatment strategies of the control group from different studies varied, which may affect the quality of the results. Third, different criteria were used to evaluate adverse events which increased the risk of publication bias. Therefore, large sample sizes and high-quality trials are needed for further exploration.

5. Conclusion

In conclusion, RTX has exhibited a favorable safety profile in the treatment of NS, characterized by a reduced incidence of AEs and infusion reactions. Notably, hematological complications were mitigated among adult patients, those with membranous nephropathy (MN), and in the context of RTX interventions at a 1000 mg dose. Additionally, close monitoring of drug interactions and potential long-term effects remains crucial to ensure optimal patient outcomes.

CRediT authorship contribution statement

Zixian Yu: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Meijin Huang:** Writing – original draft, Software, Methodology, Conceptualization. **Yunlong Qin:** Supervision, Software. **Xiayin Li:** Software. **Yueru Zhao:** Supervision. **Yuwei Wang:** Visualization, Validation. **Yumeng Zhang:** Visualization, Supervision. **Anjing**

Wang: Visualization, Validation. **Mei Han:** Validation, Supervision. **Jin Zhao:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Shiren Sun:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation, Conceptualization.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e41212.

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