Research Square

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Persistent Hypogammaglobulinemia is associated with Longer Remission Without Increased Infection Risk in Pediatric Nephrotic Syndrome After Rituximab Therapy

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Research Article

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Abstract

Background

Rituximab-induced hypogammaglobulinemia (HGG) is common in pediatric nephrotic syndrome(NS), yet its heterogeneity—particularly the distinction between transient and persistent forms and the clinical relevance of combined IgG/IgM deficiency—remains poorly understood. This study aimed to characterize HGG subtypes, identify predictors of HGG, and evaluate their associations with relapse-free survival and infection risk.

Methods

This retrospective study included pediatric patients with steroid-dependent (SD) or frequently relapsing (FR) nephrotic syndrome treated with rituximab at Beijing Children's Hospital from January 2015 to December 2023. Hypogammaglobulinemia (HGG) was defined as post-rituximab IgG/IgM below the lower limit of the age-specific reference ranges and classified as transient (THGG; resolving within 12 months) or persistent (PHGG;>12 months). Relapse-free survival was defined as no relapse wihtin 2 years post-rituximab. Multivariable logistic regression identified risk factors for THGG/PHGG, and Kaplan-Meier analysis compared relapse-free survival among non-HGG, THGG, and PHGG groups.

Results

Among 102 pediatric patients with FRNS/SDNS treated with rituximab (RTX), hypogammaglobulinemia (HGG) occurred in 74 (72.5%), comprising transient HGG (THGG; n = 33, 32.4%) and persistent HGG (PHGG; n = 41, 40.2%). Baseline serum IgG levels were significantly higher in the non-HGG group compared with both the THGG (P = 0.001) and PHGG (P = 0.006) groups. Similarly, baseline IgM levels in the non-HGG group were significantly higher than those in the THGG (P = 0.002) and PHGG (P < 0.001) groups, with the THGG group also demonstrating significantly higher IgM than the PHGG group (P = 0.005). Combined IgG/IgM deficiency was significantly more prevalent in the PHGG group [15/41 (36.6%)] than in the THGG group [2/33 (6.1%); P = 0.002].Multivariate logistic regression identified lower baseline IgG (OR = 0.026, 95% CI: 0.004–0.152, P < 0.001) and lower baseline IgM (OR = 0.690, 95% CI: 0.491–0.971, P = 0.033) as independent risk factors for THGG, alongside a greater number of RTX cycles (OR = 1.912, 95% CI: 1.073–3.407, P = 0.028). For PHGG, only the total number of RTX cycles was an independent predictor (OR = 1.616, 95% CI: 1.153–2.267, P = 0.005). Clinically, the relapse rate was inversely associated with HGG duration (non-HGG 50.0% vs. THGG 33.3% vs. PHGG 17.1%; P = 0.015), with Kaplan-Meier analysis confirming significantly superior relapse-free survival in the PHGG group versus the non-HGG group (P = 0.002). Importantly, no significant differences were observed among the three groups in the incidence of frequent infections (P = 0.640) or severe infections requiring hospitalization (P = 0.930).

Conclusion

Persistent hypogammaglobulinemia (low IgG and/or IgM) after rituximab is associated with a favorable phenotype with extended remission and no excess infection risk, highlighting its role as a clinically actionable biomarker for individualized follow-up in pediatric nephrotic syndrome.

Introduction

Nephrotic syndrome (NS) is one of the most common glomerular diseases in children, with approximately 80–90% of cases classified as steroid-sensitive at onset. However, a substantial proportion of children develop frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS), necessitating repeated courses of corticosteroids and exposure to steroid-sparing immunosuppressants[1]. Rituximab (RTX), a chimeric monoclonal antibody directed against the CD20 antigen on B lymphocytes, has emerged as a highly effective agent for maintaining remission in these challenging phenotypes. By depleting circulating $CD20^{+}$B cells, RTX significantly prolongs relapse-free intervals and reduces cumulative steroid toxicity, and is now endorsed by international guidelines as a therapeutic option for FRNS/SDNS unresponsive to conventional steroid-sparing regimens[2–3].

Hypogammaglobulinemia (HGG), defined as serum immunoglobulin levels below age-adjusted normal ranges, is a well-recognized consequence of RTX therapy[4–5]. In patients treated with RTX for autoimmune diseases, reductions in IgG, often accompanied by decreased IgM, have been consistently reported, with persistent low IgM identified in up to 30–50% of patients after repeated treatment cycles[6]. In these populations, combined IgG and IgM suppression has been linked to both sustained disease control and, in some series, increased susceptibility to serious infections, prompting recommendations for routine immunoglobulin monitoring[7]. In contrast, data on post-RTX HGG in pediatric NS remain limited. Most existing studies have focused on total IgG levels alone, while the behavior of IgM—often the first immunoglobulin to decline and the last to recover—has received comparatively little attention[8–9]. Given that children with NS may receive multiple RTX courses over several years, understanding the trajectory and clinical relevance of combined IgG and IgM suppression in this setting carries significant research and clinical value.

This study therefore aimed to systematically characterize the heterogeneity of hypogammaglobulinemia (HGG) in children with FRNS/SDNS following RTX therapy, encompassing both isolated and combined IgG/IgM deficiency patterns. Specifically, we sought to: (i) delineate the distinct immunological profiles and clinical characteristics between THGG and PHGG subgroups; (ii) identify independent predictors for the development of PHGG; (iii) evaluate the association between specific HGG subtypes and relapse-free survival (RFS) post-RTX; and (iv) determine whether persistent IgG and/or IgM deficiency confers an increased risk of clinically significant infections.

Patients and Methods

Patient population and data collection

This retrospective study included children aged between 3 and 15 years old with SDNS/FRNS who received RTX for the first time at the renal department of Beijing Children's Hospital, National Center for Children's Health, China, between January 2015 and December 2023. All pediatric patients had follow-up recurrence data for at least two years. In this study, the definitions and criteria adopted for NS, remission, relapse, frequent relapse, steroid dependency, and steroid resistance were according to the International Study of Kidney Disease in Children[10]. All patients were steroid sensitive and in remission at the time of first rituximab treatment.The exclusion criteria were: (1) Data were incomplete at both baseline and follow-up(2)The patient failed to meet the treatment protocol[3] Children with systemic diseases or infections such as tuberculosis.

HGG was defined as a serum immunoglobulin G(IgG)and/or immunoglobulin M（IgM）level of below the lower limit of the age-specific reference ranges:0–2 years,<3.50g/L;2–6 years, <4.0g/L;and >6 years,<5.0g/L.Low IgM was defined using the age-specific lower reference limits: 0–2 years,<0.3 g/L; 2–12 years,<0.40 g/L; and > 12 years, <0.48 g/L.Transient hypogammaglobulinemia (THGG) was defined as hypogammaglobulinemia resolving within 1 year; Persistent hypogammaglobulinemia (PHGG) was defined as hypogammaglobulinemia persisting for more than 1 year.Frequent infections were defined as the occurrence of three or more infection episodes within any 6 months period.Severe infection events were defined as infections that required hospitalization.

Given the retrospective nature of our study, the requirement for informed consent from patients was waived. The research was conducted following the ethical principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University(Approval No.2024-Y-035-D). All procedures performed in our studies were in accordance with these ethical standards.

Treatment protocol

Rituximab was administered during the remission period at a single dose of 375mg/m² of body surface area(maximum of 500mg). Prednisolone (PSL) was gradually tapered and then discontinued within 6 months after RTX. If a relapse occurred, standard steroid therapy was initiated and gradually tapered off within 6 months of remission.During the subsequent follow-up, the administration of RTX was determined based on the clinician's experience and joint decision-making with the patient.Maintenance therapy with an IS, such as CsA and MMF, was continued to prevent post-RTX relapse for at least 6 months. All immunosuppressive regimens adhered to the 2023 IPNA clinical practice recommendations for steroid-sensitive nephrotic syndrome in children（10）. Prophylactic sulfamethoxazole-trimethoprim was also orally administered during RTX treatment to prevent pneumocystis pneumonia.

Data collection and analysis

The study period extended for a minimum of 24 months following the initial rituximab (RTX) infusion. Data were retrospectively extracted from electronic medical records of 102 patients. Baseline demographic and clinical characteristics—including age, sex, weight, and prior immunosuppressive therapies (CTX, CsA, TAC, MMF)—were recorded at the time of the first RTX dose. Baseline laboratory assessments comprised serum immunoglobulins (IgA, IgG, IgM) and comprehensive lymphocyte subset profiling (CD19+, naïve, transitional, memory B cells, plasmablasts, CD3+, CD4+, CD8+, and NK cells).During follow-up, serum IgG, IgM, and CD19 + B-cell counts were routinely assessed approximately every 3 months, with additional testing performed as clinically indicated. Other follow-up variables included the cumulative number of RTX cycles, relapse status (primary outcome: time to first relapse), and the incidence of frequent or severe infections throughout the observation period.

Statistical analysis

Continuous variables were evaluated for normality using the Shapiro-Wilk test. Normally distributed data were expressed as means ± standard deviations (SDs) and compared among three groups using one-way analysis of variance (ANOVA). Non-normally distributed continuous variables were presented as medians with interquartile ranges (IQRs). For comparisons among three groups, the Kruskal-Wallis H test was employed; subsequently, post-hoc pairwise comparisons were conducted using the Mann-Whitney U test, with P values adjusted for multiple testing using the Bonferroni correction. Categorical variables were summarized as frequencies and percentages,

and intergroup differences were analyzed using the Pearson chi-square test or Fisher's exact test, as appropriate.Relapse-free survival was estimated using the Kaplan-Meier method, and overall differences in survival curves among groups were compared using the log-rank test. When significant overall differences were identified, post-hoc pairwise log-rank tests were performed to determine specific intergroup differences, and the resulting P values were similarly adjusted using the Bonferroni correction to control the family-wise error rate.All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A two-sided P value < 0.05 was considered statistically significant for overall comparisons, whereas the significance threshold for post-hoc pairwise comparisons was adjusted according to the number of comparisons (P < 0.0167 for three pairwise comparisons).

Results

Baseline Characteristics and Incidence of Hypogammaglobulinemia

A total of 102 pediatric patients with FRNS/SDNS who received rituximab (RTX) therapy were included in this study. Hypogammaglobulinemia (HGG) was observed in 74 patients (72.5%). Based on the duration of IgG and/or IgM recovery, patients were categorized into three groups: non-HGG (n = 28, 27.5%), transient HGG (THGG; n = 33, 32.4%), and persistent HGG (PHGG; n = 41, 40.2%). Demographic characteristics were comparable among the three groups, including male sex [21/28 (75.0%) vs. 25/33 (75.8%) vs. 27/41 (65.9%), P = 0.576], age at initial RTX [10.3 (8.0–14.2) vs. 8.9 (7.7–11.9) vs. 9.1 (7.7–11.5) years, P = 0.372], and body weight [42.4 (26.6–59.0) vs. 34.0(27.5–54.9) vs. 34.5 (27.0–48.9) kg, P = 0.870]. Prior to the initial RTX infusion, the use of concomitant immunosuppressants (cyclophosphamide, cyclosporin A, tacrolimus, or mycophenolate mofetil) did not differ significantly across groups (all P > 0.05).

In contrast, significant differences were identified in baseline immunological profiles and post-RTX treatment parameters. Regarding baseline immunoglobulins, the non-HGG group exhibited significantly higher serum IgG levels [7.3 (5.9–10.0) g/L] compared with both the THGG [5.0 (3.2–7.7) g/L; P = 0.001] and PHGG [5.9 (5.1–7.6) g/L; P = 0.006] groups. Similarly, baseline serum IgM levels in the non-HGG group [2.14 (1.44–2.53) g/L] were significantly higher than those in the THGG [1.44 (1.18–1.84) g/L; P = 0.002] and PHGG [1.10 (0.95–1.46) g/L; P < 0.001] groups; notably, the THGG group also demonstrated significantly higher IgM levels than the PHGG group (P = 0.005). Conversely, the baseline percentage of CD19 + B cells was significantly lower in both the non-HGG [10.3% (7.3%–17.4%); P = 0.038] and THGG [13.6% (10.0%–22.0%); P = 0.016] groups compared with the PHGG group [15.7% (10.3%–24.0%)]. Following the initial RTX treatment, the proportion of patients continuing cyclosporin A maintenance was significantly higher in the non-HGG group [13/28 (46.4%)] than in the PHGG group [6/41 (14.6%)] (P = 0.004). Furthermore, patients in the non-HGG group required significantly fewer total RTX cycles [2.0 (1.0–3.0)] compared to those with PHGG [3.0 (2.0–4.0)] (P = 0.004). These findings are summarized in Table 1.

Table 1
Clinical characteristics, laboratory parameters, and outcomes among Non-HGG, THGG, and PHGG groups

Parameter	Overall (n = 102)	Non-HGG group (n = 28)	THGG group (n = 33)	PHGG group (n = 41)	*p*-value
Demographics					
Male(%)	73(71.6)	21(75.0)	25(75.8)	27(65.9)	0.576
Age(years)	9.3[7.9,12.5]	10.3[8.0,14.2]	8.9[7.7,11.9]	9.1[7.7,11.5]	0.372
Weight(kg)	35.6[27.0,50.0]	42.4[26.6,59.0]	34.0[27.5,54.9]	34.5[27.0,48.9]	0.870
IS before initial RTX					
CTX n (%)	9(8.8)	2(7.1)	5(15.2)	2(4.9)	0.282
CsA n (%)	30(29.4)	10(35.7)	10(30.3)	10(24.3)	0.593
TAC n (%)	35(34.3)	9(32.1)	11(33.3)	15 (36.6)	0.920
MMF n (%)	17(16.7)	3(10.7)	5(15.2)	9 (22.0)	0.451
None n (%)	13(12.7)	5(17.9)	3(9.1)	5 (12.2)	0.587
IS after initial RTX					
CsA n (%)	27(26.5)	13(46.4)‡	8(24.2)	6(14.6)	0.012
TAC n (%)	27(26.5)	5(17.9)	9(27.3)	13(31.7)	0.679
MMF n (%)	18(17.6)	4(14.3)	4(12.1)	10(24.4)	0.334
None n (%)	30(29.4)	6(21.4)	12(36.4)	12(29.3)	0.443
Laboratory data					
IgA(g/L)	1.35[0.89,2.31]	1.75[0.93,2.72]	1.59[0.91,2.75]	1.26[0.84,1.70]	0.139
IgG(g/L)	5.9[4.7,7.7]	7.3[5.9,10.0]†,‡	5.0[3.2,7.7]	5.9[5.1,7.6]	0.005
IgM(g/L)	1.38[1.02,2.04]	2.14[1.44,2.53]†,‡‡	1.44[1.18,1.84]‡	1.10[0.95,1.46]	<0.001
CD19 + B cells(%L)	13.0[9.0,20.1]	10.3[7.3,17.4]‡	13.6[10.0,22.0]‡	15.7[10.3,24.0]	0.026
Naïve(%BL)	46.8[22.2,60.1]	47.1[24.5,61.8]	42.0[22.0,60.2]	47.3[22.2,60.1]	0.884
Transitional(%BL)	7.5[4.0,15.0]	10.0[5.5,17.3]	6.3[3.7,11.0]	7.7[2.6,15.0]	0.257
Memory(%BL)	19.0[12.0,26.6]	20.7[14.2,26.0]	17.9[11.0,25.3]	20.0[11.0,32.3]	0.295
Plasmablasts(%BL)	1.5[0,2.0]	1.3[0,2.0]	1.0[0,1.95]	1.5[0.4,2.2]	0.364
CD3 + T cells(%L)	77.8[73.5,83.9]	75.5[73.5,84.5]	79.7[74.1,85.0]	77.2[70.7,81.9]	0.212
CD4 + T cells(%L)	39.1[34.2,46.0]	36.3[33.8,43.7]	40.3[34.6,51.4]	40.6[34.4,45.5]	0.185
CD8 + T cells(%L)	29.3[24.5,34.1]	29.3[24.6,34.0]	30.5[24.0,36.1]	28.8[24.7,33.2]	0.892
NK cells(%L)	8.1[5.6,12.7]	9.0[5.0,13.6]	8.7[5.0,12.1]	7.2[6.3,10.7]	0.840

Parameter	Overall (n = 102)	Non-HGG group (n = 28)	THGG group (n = 33)	PHGG group (n = 41)	*p*-value
Follow up data					
Total cycles of RTX treatment	3.0[2.0,3.25]	2.0[1.0,3.0]‡	3.0[2.0,3.5]	3.0[2.0,4.0]	0.004
Relapse after RTX treatment,n (%)	32(31.3)	14(50)‡	11(33.3)	7(17.1)	0.015
Frequent Infections n (%)	7(6.9)	3(10.7)	2(6.1)	2(4.9)	0.640
Severe Infections n (%)	4(4.0)	1(3.6)	1(3.0)	2(4.9)	0.930

HGG, hypogammaglobulinemia; THGG, transient hypogammaglobulinemia; PHGG, persistent hypogammaglobulinemia; IS, immunosuppressive agents; RTX, rituximab; CTX, cyclophosphamide; CsA, cyclosporin A; TAC, tacrolimus; MMF, mycophenolate mofetil; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; %L, percentage of lymphocytes; %BL, percentage of B lymphocytes; NK, natural killer.

† $p < 0.05$ vs. THGG group; ‡ $p < 0.05$ vs. PHGG group; ‡ ‡ $p < 0.001$ vs. PHGG group.

Immunoglobulin Deficiency Patterns in HGG Subgroups

The subtypes of hypogammaglobulinemia differed significantly between the THGG and PHGG groups (Table 2). Isolated IgG deficiency was the predominant pattern in the THGG group [29/33 (87.9%)], whereas combined IgG/IgM deficiency was significantly more prevalent in the PHGG group [15/41 (36.6%)] than in the THGG group [2/33 (6.1%); P = 0.002]. Additionally, isolated IgM deficiency was observed more frequently in the PHGG group [10/41 (24.4%)] compared to the THGG group [2/33 (6.1%); P = 0.033]. Notably, isolated IgG deficiency remained the most common subtype in the PHGG group [16/41 (39.0%)], although its proportion was significantly lower than that in the THGG group (P < 0.001).

Table 2
Distribution of immunoglobulin deficiency patterns in THGG and PHGG groups

Parameter	THGG group (n = 33)	PHGG group (n = 41)	p-value
IgG↓IgM↓	2(6.1)	15(36.6)	0.002
IgG↓IgM-	29(87.9)	16(39.0)	<0.001
IgG-IgM↓	2(6.1)	10(24.4)	0.033

THGG, transient hypogammaglobulinemia; PHGG, persistent hypogammaglobulinemia; IgG, immunoglobulin G; IgM, immunoglobulin M. ↓, indicates serum level below the lower limit of the age-specific reference range; -, indicates serum level within the age-specific reference range.

Independent Predictors of Hypogammaglobulinemia

Multivariate logistic regression analysis was performed to identify independent risk factors for the development of THGG and PHGG (Table 3). For the occurrence of THGG, lower baseline serum IgG levels (OR = 0.026, 95% CI: 0.004–0.152, P < 0.001) and lower baseline IgM levels (OR = 0.690, 95% CI: 0.491–0.971, P = 0.033) were identified as independent risk factors, indicating that patients with diminished pre-treatment immunoglobulin reserves are at a significantly higher risk. Additionally, a greater total number of RTX treatment cycles was independently

associated with an increased risk of THGG (OR = 1.912, 95% CI: 1.073–3.407, P = 0.028). Regarding PHGG, the total number of RTX treatment cycles emerged as the sole independent predictor (OR = 1.616, 95% CI: 1.153–2.267, P = 0.005), demonstrating that repeated RTX administration significantly increases the risk of persistent hypogammaglobulinemia. Other variables, including CsA maintenance and baseline CD19 + B-cell percentages, did not show independent predictive value in either model. Seven patients in the PHGG group developed persistent hypogammaglobulinemia despite receiving only a single RTX dose throughout their entire disease course.

Table 3
Risk factors for THGG and PHGG identified by multivariate logistic regression analysis

	THGG			PHGG		
	OR	**95%CI**	***p* value**	**OR**	**95%CI**	***p* value**
CsA	0.361	0.071–1.822	0.217	1.887	0.602–5.916	0.276
IgG	0.026	0.004–0.152	<0.001	0.893	0.761–1.048	0.165
IgM	0.690	0.491–0.971	0.033	0.989	0.486–2.009	0.975
CD19+	1.062	0.950–1.186	0.290	0.933	0.881–1.187	0.134
Total cycles of RTX treatment	1.912	1.073–3.407	0.028	1.616	1.153–2.267	0.005

OR, odds ratio; CI, confidence interval; IgG, immunoglobulin G; IgM, immunoglobulin M; CsA, cyclosporin A; RTX, rituximab. Reference group for categorical variables was non-exposure. Continuous variables were analyzed per unit increase.

Association Between Hypogammaglobulinemia and Clinical Outcomes

The overall relapse rate following RTX treatment was 31.3% (32/102). A significant inverse relationship was observed between HGG status and relapse rate. The relapse rate was highest in the non-HGG group (50.0%, 14/28), followed by the THGG group (33.3%, 11/33), and lowest in the PHGG group (17.1%, 7/41) (P = 0.015).To further evaluate the time-to-event outcomes, Kaplan-Meier analysis of relapse-free survival was performed (Fig. 2). Pairwise comparisons using the log-rank test revealed that the PHGG group had a significantly higher relapse-free survival rate compared to the non-HGG group (log-rank χ^2 = 10.05, P = 0.002). However, no statistically significant differences were observed between the PHGG and THGG groups (log-rank χ^2 = 2.973, P = 0.085) or between the THGG and non-HGG groups (log-rank χ^2 = 1.214, P = 0.271). These findings suggest that sustained lower immunoglobulin levels post-RTX were associated with prolonged remission.

In terms of safety, there were no statistically significant differences in the incidence of frequent infections among the non-HGG (10.7%), THGG (6.1%), and PHGG (4.9%) groups (P = 0.640). Similarly, the rate of severe infections requiring hospitalization was comparable across the three groups (3.6% vs. 3.0% vs. 4.9%; P = 0.930). Thus, neither THGG nor PHGG conferred an increased risk of severe infectious events in this cohort.

Discussion

In this study, we systematically characterized hypogammaglobulinemia (HGG) following rituximab (RTX) therapy in 102 children with FRNS/SDNS. We found that persistent HGG (PHGG) was associated with improved relapse-free

survival without increased overall infection risk, partially aligning with Cals et al. who linked prolonged B-cell depletion to both extended remission and HGG[11]. However, our data extend these findings by revealing significant individual heterogeneity: seven patients developed PHGG after only a single RTX dose throughout their entire disease course, despite cumulative exposure being the primary predictor in our model. This suggests that beyond treatment intensity, individual susceptibility—potentially driven by genetic or immunological factors governing B-cell reconstitution—plays a critical role in PHGG pathogenesis, highlighting the need for personalized risk assessment rather than relying solely on cumulative dosing metrics.

In our cohort, the overall incidence of HGG—defined as low IgG and/or low IgM—was 72.5%, comprising PHGG in 40.2% and transient HGG (THGG) in 32.4% of patients. Previous studies have reported widely varying post-RTX HGG rates ranging from 8% to 61%[12–14]. Notably, this seemingly higher incidence in our study is largely attributable to our broader diagnostic criteria. When applying the conventional definition of isolated low IgG used in most prior literature, the overall HGG rate in our cohort recalculates to 60.7% (with THGG at 30.3% and PHGG at 30.4%), which aligns well with previously reported figures.

Immunoglobulin M (IgM), characterized by its μ heavy chains, is the first antibody class expressed on developing B cells and secreted during the early phase of primary immune responses. Beyond its role as an initial defense against antigens, IgM exerts broad immunoregulatory functions, including B cell development regulation, apoptotic cell clearance, modulation of inflammation and autoimmunity, and antitumor immunity[7, 15]. The role of immunoglobulin M (IgM) in nephrotic syndrome (NS) presents a compelling profile. Some studies have reported elevated serum IgM levels during the early stages of pediatric NS[16]. Independently, renal biopsy specimens from a subset of children with NS reveal IgM deposition, which is associated with steroid-resistant or steroid-dependent phenotypes[17]. Furthermore, a recent study reported that IgM-positive anti-nephrin antibodies account for 39.1% of cases, underscoring the active involvement of IgM in NS pathogenesis[18]. In the present cohort, low serum IgM was observed in 28.4% (29/102) of patients, constituting 61% of the persistent hypogammaglobulinemia (PHGG) group. This aligns with previous reports indicating that the incidence of low IgM following rituximab (RTX) therapy can reach up to 46%[8], suggesting that systemic IgM deficiency is not uncommon in RTX-treated children with NS and may be intricately linked to disease pathophysiology.

Notably, compared with IgG depletion, the decline in serum IgM exhibited a delayed onset, and a substantial proportion of patients maintained persistently low IgM levels even after B-cell reconstitution at approximately six months post-RTX[19]. This prolonged deficiency is mechanistically explained by the preferential depletion of naïve and unswitched memory B cells—the key precursors for IgM-producing short-lived plasma cells—which repopulate slowly following RTX therapy. Unlike IgG and IgA, which are sustained by CD20-negative long-lived plasma cells residing in the bone marrow, IgM lacks this protected reservoir, rendering its recovery contingent upon de novo B-cell maturation rather than pre-existing plasma cell survival[7]. Consistent with this vulnerability in reconstitution kinetics, our data further identified repeated RTX administration as a major driver of sustained IgM hypogammaglobulinemia, likely due to cumulative suppression of the nascent B-cell compartment before adequate IgM-secreting cell differentiation can occur. A similar phenomenon of persistent IgM deficiency despite B-cell recovery has been documented in other autoimmune diseases[7]. Intriguingly, in patients with rheumatoid arthritis treated with RTX, persistent low IgM has been correlated with sustained disease remission[20]. The unique temporal dynamics of IgM and its potential association with prolonged remission warrant further investigation.

Some investigators have proposed that pre-RTX hypogammaglobulinemia (HGG) reflects extensive prior immunosuppressive exposure in refractory disease, thereby conferring an elevated relapse risk [4, 9]. In contrast, we found that the type of pre-RTX immunosuppressant did not influence relapse risk, and children with PHGG paradoxically exhibited lower relapse rates. This discrepancy likely stems from our exclusive inclusion of patients with steroid-sensitive nephrotic syndrome (SSNS). Unlike the refractory cohorts in prior studies [13], our SSNS population lacked prolonged immunosuppressive histories, thereby minimizing confounding by heavy refractory disease burden and cumulative immunosuppressive toxicity. Consequently, our findings do not negate the well-established premise that prolonged immunosuppressive therapy profoundly impairs immunoglobulin homeostasis [21].

Despite the profound humoral impairment observed, particularly the high prevalence of concurrent IgM deficiency, we found no significant increase in either the frequency or severity of infections among patients with HGG. This aligns with several previous studies failing to establish a direct correlation between RTX-induced HGG and elevated infection risk[22-25], suggesting that when infections do occur, they may be attributable to concomitant neutropenia rather than isolated HGG. These findings underscore the remarkable resilience of the adaptive immune system: qualitative compensation may occur wherein residual immunoglobulins, despite being quantitatively low, retain robust functionality with adequate affinity and neutralizing capacity[26]. Consequently, rather than adopting a blanket approach to IVIG replacement based solely on laboratory thresholds, future studies should focus on phenotyping specific HGG subpopulations to identify those who truly derive clinical benefit from immunoglobulin supplementation[1,22]. Collectively, these findings reframe RTX-induced HGG—particularly when defined by sustained post-treatment low IgG and/or IgM—from a mere adverse event requiring correction to a potential biomarker of adequate therapeutic effect.

Several limitations of this study warrant consideration. First, as a single-center retrospective analysis, our findings may be influenced by institution-specific treatment protocols and patient demographics, potentially limiting their generalizability to other clinical settings. Second, the relatively short follow-up duration precludes definitive conclusions regarding long-term immunological recovery and late-onset infectious complications beyond the observation window. Third, the absence of standardized serial measurements for antigen-specific antibody titers and B-cell subsets restricts our ability to precisely delineate the qualitative functional compensation underlying hypogammaglobulinemia.Finally, while we identified persistent hypogammaglobulinemia as a surrogate marker for reduced relapse, the causal relationship between B-cell depletion depth and sustained remission requires validation in prospective multicenter cohorts with extended follow-up and comprehensive immune profiling. Despite these constraints, our data provide clinically relevant insights into the safety profile and biological significance of rituximab-induced hypogammaglobulinemia in pediatric nephrotic syndrome.

In conclusion, our findings reframe rituximab-induced hypogammaglobulinemia in pediatric nephrotic syndrome as a potential biomarker of effective B-cell depletion rather than an isolated safety concern. The absence of increased infection risk, even with concurrent IgM deficiency, suggests that residual humoral immunity retains sufficient functional capacity, challenging the routine use of IVIG replacement. Future prospective multicenter cohorts with longitudinal immune profiling are essential to validate these observations and define precise criteria for targeted immunoglobulin supplementation.

Declarations

Conflict of interest

All authors declare no real or perceived conflicts of interest that could affect the study design, collection, analysis and interpretation of data, writing of the report, or the decision to submit

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Authors’contribution

Study conception and design were performed by Chen Ling. Patient recruitment and clinical data collection were carried out by Zhi Chen, Yue Xi, Lei Lei, and Hejia Zhang. Statistical analysis was performed by Lin Hua. Chen Ling drafted the original manuscript. Xiaorong Liu supervised the study and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Figures

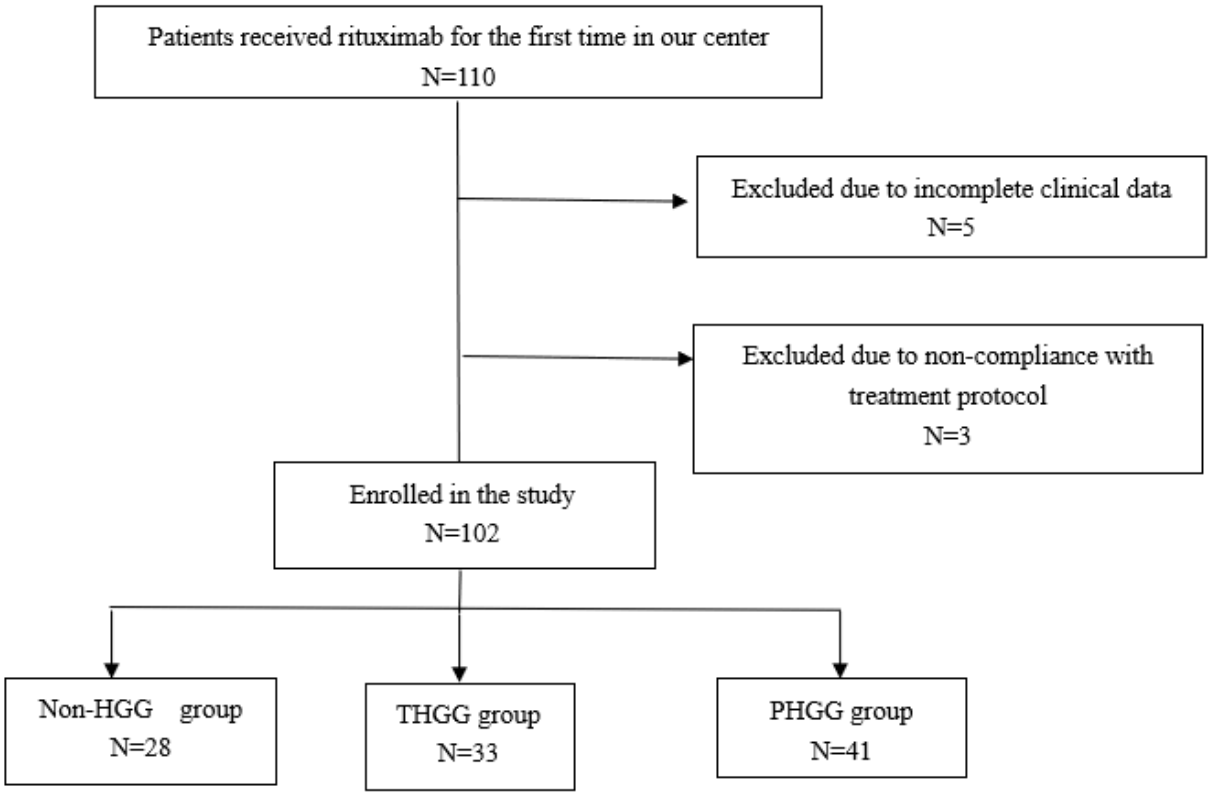


Figure 1

Flow diagram of the study population.

SDNS, steroid-dependent nephrotic syndrome; FRNS, frequent relapsing nephrotic syndrome；HGG： Hypogammaglobulinemia；THGG：Transient hypogammaglobulinemia；PHGG, Persistent hypogammaglobulinemia.

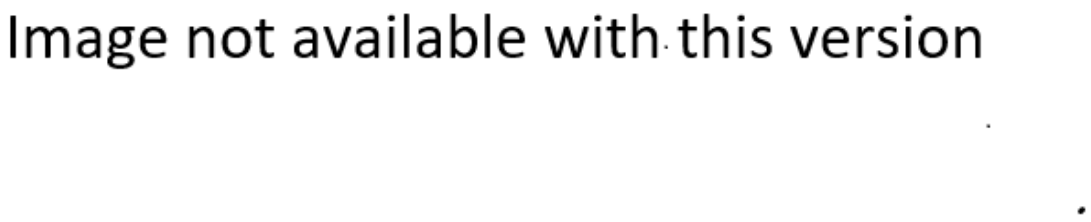


Figure 2

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