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Disease Status at Belimumab Initiation and Clinical Outcomes in Childhood-Onset Lupus Nephritis: A Single-Center Retrospective Cohort Study

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Abstract

Objective: To investigate whether disease status at belimumab (BLM) initiation was associated with clinical outcomes in children with childhood-onset lupus nephritis (cLN).

Methods: This single-center retrospective cohort study included children and adolescents with active cLN treated with intravenous BLM plus standard therapy at the Affiliated Hospital of Qingdao University between January 2020 and April 2026. Patients were classified into a newly diagnosed group (BLM initiation within 12 weeks after cLN diagnosis) or a relapsed group (BLM initiation within 12 weeks after LN relapse following renal remission). The primary outcomes were complete renal response (CRR) and partial renal response (PRR). Secondary outcomes included lupus low disease activity state (LLDAS), DORIS remission, disease activity, glucocorticoid dose reduction, and safety.

Results: Thirty-six patients were included (25 newly diagnosed and 11 relapsed). At 12 months, CRR was achieved more frequently in the newly diagnosed group than in the relapsed group [94.7% (18/19) vs. 55.6% (5/9), $P=0.026$], as was LLDAS attainment [73.7% (14/19) vs. 22.2% (2/9), $P=0.017$]. Age-adjusted Cox models showed higher hazards of achieving LLDAS (HR=4.224, 95% CI 1.240–14.392, $P=0.021$) and DORIS remission (HR=4.552, 95% CI 1.265–16.379, $P=0.020$) in newly diagnosed patients. Disease activity, proteinuria, complement levels, and glucocorticoid doses improved in

both groups, with greater improvement and faster steroid reduction in the newly diagnosed group.

Conclusion: Among children with cLN treated with BLM-containing regimens, disease status at treatment initiation was associated with subsequent treatment trajectories. Patients receiving BLM during the newly diagnosed phase demonstrated more favorable achievement of renal response and treatment targets.

1 Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement. Childhood-onset SLE (cSLE) accounts for approximately 15%-20% of all SLE cases [1]. Compared with adult-onset SLE, cSLE is usually associated with more abrupt onset, higher disease activity, more frequent major organ involvement, and poorer prognosis [2]. Lupus nephritis (LN) is among the most serious manifestations of SLE and affects more than 50% of patients during the disease course. More than 15% of patients with LN ultimately progress to end-stage kidney disease (ESKD), contributing substantially to morbidity and adverse long-term outcomes [3,4]. Although glucocorticoids (GCs) and immunosuppressive agents have improved remission rates, 10%-50% of patients still experience renal relapse [5]. Children with relapsing LN may accumulate irreversible renal and extrarenal damage, respond less favorably to conventional immunosuppression, and face greater treatment-related toxicity, making long-term disease control particularly challenging [6].

BLM is the first biologic agent approved for SLE. It inhibits soluble B-cell activating factor (BAFF), thereby reducing survival signals for autoreactive B cells, limiting autoantibody production, and attenuating immune-mediated inflammation [7]. In adults with SLE and LN, adding BLM to standard therapy has been shown to reduce disease activity, improve renal response, and lower the risk of flares or renal-related events [8–10]. The PLUTO trial provided randomized evidence supporting the efficacy and safety of BLM in cSLE, with potential benefit in patients with renal involvement [11].

However, evidence for BLM specifically in cLN remains limited. Most available pediatric studies have compared standard therapy alone with standard therapy plus BLM [12,13], whereas no studies have specifically compared treatment outcomes between newly diagnosed patients and those receiving BLM after relapse. Newly diagnosed and relapsed cLN may differ in disease duration, accumulated renal injury, immunologic activity, and prior treatment exposure; therefore, their responses to BLM may not be equivalent.

Therefore, we compared clinical outcomes after BLM plus standard-of-care therapy between patients with newly diagnosed and relapsed cLN to determine whether initiation at diagnosis versus after relapse was associated with different renal responses, treatment-target attainment, glucocorticoid tapering, and safety outcomes.

2 Materials and methods

2.1 Study Design and participants

This single-center retrospective cohort study included children and adolescents treated at the Affiliated Hospital of Qingdao University between January 2020 and April 2026 who were diagnosed with active cLN and received BLM in combination with standard-of-care therapy.

This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Approval No. QYFY WZLL 50300) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient's legal guardians prior to data collection and publication.

2.1.1 Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) age 5-18 years; (2) fulfillment of the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [14] or the 2019 EULAR/ACR classification criteria for SLE [15]; (3) diagnosis of LN according to the Evidence-Based Guideline for the Diagnosis and Treatment of Lupus Nephritis issued by the Nephrology Subspecialty Group of the Chinese Society of Pediatrics in 2016 [16]; and (4) received kidney biopsy and histopathological evaluation within 3 months before BLM treatment, with LN classified according to the 2003 and 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification systems [17,18].

Exclusion criteria were: (1) incomplete clinical data or follow-up duration shorter than 6 months; and (2) exposure to biologic agents within 12 months before BLM initiation.

2.1.2 Patient Grouping

Patients were assigned to the newly diagnosed or relapsed group according to disease status at BLM initiation. The newly diagnosed group included patients with newly diagnosed cLN who started BLM within 12 weeks after diagnosis. The relapsed group included patients with previously diagnosed cLN who relapsed after renal remission and started BLM within 12 weeks after relapse.

LN relapse was defined according to previous studies and guideline recommendations as any of the following: (1) an increase in 24-hour urinary protein excretion from <0.2 g/day at baseline to >1.0 g/day, from 0.2 - 1.0 g/day at baseline to >2.0 g/day, or a >2 -fold increase when baseline proteinuria was >1.0 g/day; (2) an increase in serum creatinine of $\geq 20\%$ from baseline or ≥ 0.3 mg/dL accompanied by proteinuria, hematuria, or red blood cell casts; or (3) new-onset glomerular hematuria accompanied by proteinuria or red blood cell casts. Proteinuria was assessed using 24-hour urinary protein excretion or the urine protein-to-creatinine ratio (UPCR) [19].

2.2 Treatment Protocol

All participants received BLM plus standard-of-care therapy. BLM was administered intravenously at 10 mg/kg at Weeks 0, 2, and 4 and every 4 weeks thereafter. Standard-of-care therapy was individualized according to disease severity, physician assessment, and shared decision-making with guardians, and consisted of GCs combined with immunosuppressive agents, including mycophenolate mofetil (MMF), tacrolimus (TAC), or multitarget therapy (MMF plus TAC). During induction, one or two courses of high-dose intravenous methylprednisolone pulse therapy were permitted. Written informed consent for BLM and standard-of-care therapy was obtained from parents or legal guardians.

2.3 Data Collection and Follow-up

Demographic, clinical, laboratory, and treatment-related data were retrospectively extracted from electronic medical records. Baseline was defined as the date of BLM initiation. Baseline variables included demographic characteristics, renal pathological class, extrarenal organ involvement, disease activity, renal function and proteinuria-related parameters, immunologic markers, and treatment regimens at the time of BLM initiation.

Clinical and laboratory data were collected at baseline and every 3 months after treatment initiation, including SLEDAI-2K score, daily GC dose, 24-hour urinary protein excretion, serum albumin, complement levels, immunoglobulin G (IgG), and estimated glomerular filtration rate (eGFR).

For patients younger than 16 years, eGFR was calculated using the modified Schwartz formula [20]; for those aged 16 years or older, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was applied [21].

2.4 Outcomes

The primary outcomes were complete renal response (CRR) and partial renal response (PRR) at 12 months after BLM initiation. Definitions were based on the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Lupus Nephritis [22]. CRR was defined as 24-hour urinary protein excretion <0.5 g/1.73 m²/day, <300 mg/m²/day, or UPCR <0.5 g/g, accompanied by stable or improved kidney function, defined as eGFR within 10%-15% of baseline or within the normal age-adjusted range. PRR was defined as a $\geq 50\%$ reduction in proteinuria from baseline and a decrease in UPCR to <3.0 g/g, accompanied by stable or improved kidney function, defined as eGFR within 10%-15% of baseline or within the normal age-adjusted range.

Secondary outcomes included: (1) attainment of lupus low disease activity state (LLDAS) and Definitions of Remission in Systemic Lupus Erythematosus (DORIS) remission at 12 months; (2) changes in SLEDAI-2K scores and daily GC dose; (3) changes in 24-hour urinary protein excretion, serum albumin, eGFR, immunoglobulin G (IgG), and complement levels; and (4) LN relapse, rescue therapy, and adverse events.

LLDAS was defined as a SLEDAI-2K score ≤ 4 , no activity in major organ systems, no new disease activity compared with the previous assessment, a Physician Global Assessment (PGA) score ≤ 1 , a prednisone-equivalent dose ≤ 7.5 mg/day, and standard maintenance doses of immunosuppressive agents and biologic therapies. DORIS remission was defined as a clinical SLEDAI-2K score of 0 (excluding serological parameters), a PGA score ≤ 0.5 , a prednisone-equivalent dose ≤ 5 mg/day, and standard maintenance doses of immunosuppressive agents and biologic therapies [15].

Rescue therapy was defined as escalation beyond the planned induction or maintenance regimen because of LN relapse, persistent failure to achieve LLDAS, or inadequate treatment response. It included an increase in GC dose, addition or intensification of systemic immunosuppressive agents, or administration of intravenous immunoglobulin.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS version 27.0.1, and figures were generated using GraphPad Prism version 10.1.2. Normally distributed continuous variables are presented as mean $\pm$ SD and were compared using the independent-samples t-tests. Non-normally distributed continuous variables are presented as median (IQR) and were compared using nonparametric tests. Categorical variables are presented as numbers (percentage)(n (%)) and were compared using Fisher exact tests. Cox proportional hazards models adjusted for age were used to compare time to CRR, PRR, LLDAS, and DORIS remission between groups. Age-adjusted linear mixed-effects models were used to evaluate longitudinal changes in repeated measures within and between groups over time. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

3 Results

3.1 General information and baseline characteristics

Thirty-six patients were included: 25 in the newly diagnosed group and 11 in the relapsed group (**Figure 1**). Baseline characteristics are summarized in **Table 1**. Sex, body weight, 24-hour urinary protein excretion, autoantibody profiles, frequency of hypocomplementemia, organ involvement, renal histopathological class, GC dose, and immunosuppressive regimens were comparable between groups (all $p > 0.05$). Compared with the relapsed group, the newly diagnosed group was younger and had shorter disease duration, higher SLEDAI-2K scores, lower complement levels, lower eGFR, and a higher frequency of acute kidney injury (all $p < 0.05$). Although not statistically significant, 24-hour urinary protein excretion was numerically higher in the relapsed group than in the newly diagnosed group. In addition, intravenous methylprednisolone pulse therapy was less frequently used in the relapsed group than in the newly diagnosed group.

Given that patients in the relapsed group had received previous treatment before BLM initiation, their prior disease course and treatment exposure were further characterized.

These patients in the relapsed group had a mean disease duration of 75.4 ± 30.5 months before BLM initiation and had experienced previous renal flares and immunosuppressive treatments, including cyclophosphamide induction in 6 patients (54.5%) and MMF maintenance therapy in 10 patients (90.9%). The mean duration of glucocorticoid exposure was 52.6 ± 21.7 months. At relapse, BLM was initiated mainly for relapse prevention or glucocorticoid tapering. Detailed previous disease course and treatment exposure are summarized in Supplementary Table 1.

3.2 Primary outcome

Primary and secondary outcomes are summarized in **Table 2**. At 12 months after BLM initiation, the CRR rate was higher in the newly diagnosed group than in the relapsed group [94.7% (18/19) vs. 55.6% (5/9), $p=0.026$]. The between-group difference persisted from Month 9 onward ($P<0.05$; **Figure 2A**). PRR at 12 months did not differ significantly between groups [94.7% (18/19) vs. 66.7% (6/9), $p=0.084$; **Figure 2B**]. In age-adjusted Cox proportional hazards models, the newly diagnosed group showed numerically higher hazards of achieving CRR (HR=2.304, 95% CI 0.776-6.841; $p=0.113$) and PRR (HR=1.420, 95% CI 0.562-3.589; $p=0.458$) than the relapsed group during the 24-month follow-up, suggesting a tendency toward earlier renal response; however, neither association reached statistical significance (**Figure 2C, D**).

3.3 Secondary outcomes

At 12 months after BLM initiation, the LLDAS rate was higher in the newly diagnosed group than in the relapsed group [14/19 (73.7%) vs. 2/9 (22.2%), $p=0.017$]. This difference persisted through Month 18 ($p<0.05$; **Figure 3A**). DORIS remission at 12 months did not differ significantly between groups [36.8% (7/19) vs. 11.1% (1/9), $p=0.214$; **Figure 3B**]. In age-adjusted Cox proportional hazards models, the newly diagnosed group had higher hazards of achieving LLDAS (HR=4.224, 95% CI 1.240-14.392; $p=0.021$) and DORIS remission (HR=4.552, 95% CI 1.265-16.379; $p=0.020$) than the relapsed group during the 24-month follow-up, indicating earlier attainment of these treatment targets (**Figure 3C, D**).

3.4 SLEDAI-2K Scores and daily dose of GC

SLEDAI-2K scores decreased significantly from baseline in both groups throughout follow-up ($p<0.001$). In the newly diagnosed group, SLEDAI-2K scores continued to decline during the first 9 months after BLM initiation (all $P<0.05$), whereas in the relapsed group a significant reduction was observed only during the first 3 months (all $p<0.05$). Furthermore, SLEDAI-2K scores were significantly lower in the newly diagnosed group between Months 12 and 18 (all $p<0.05$). In age-adjusted linear mixed-effects models, the decline in SLEDAI-2K score was more rapid in the newly diagnosed group than in the relapsed group ($p<0.001$; **Figure 4A**).

Daily GC doses decreased significantly during the first 9 months of treatment in both

groups (all $p < 0.05$). Age-adjusted linear mixed-effects modeling showed a greater reduction in GC dose in the newly diagnosed group than in the relapsed group ($p < 0.01$). Although GC doses were numerically lower in the newly diagnosed group from Month 6 onward, the between-group differences at individual time points were not statistically significant (**Figure 4B**).

3.5 Changes of clinical indicators

Both 24-hour urinary protein excretion and serum albumin levels improved significantly from baseline within the first 3 months in both groups (all $p < 0.05$). Improvement was slower in the relapsed group. Significant between-group differences in 24-hour urinary protein excretion were observed from Months 3 to 12, whereas differences in serum albumin persisted through Month 15 (all $p < 0.05$; **Figure 5A, B**).

Serum C3 and C4 levels increased significantly from baseline within the first 3 months in both groups (all $p < 0.001$) and remained stable thereafter. Complement recovery was more rapid in the newly diagnosed group, with higher overall C3 and C4 levels during follow-up ($p < 0.05$). C3 differed significantly at Months 9 and 15, and C4 differed significantly at Month 12 (all $p < 0.05$; **Figure 5C, D**).

In the relapsed group, eGFR remained within the normal range throughout follow-up. In the newly diagnosed group, eGFR increased significantly from baseline within the first 3 months ($p < 0.001$) and remained stable thereafter. eGFR did not differ significantly between groups at any follow-up time point (**Figure 5E**).

Serum IgG levels decreased significantly from baseline within the first 3 months in both groups (all $p < 0.05$), followed by a gradual upward trend. Although IgG levels were consistently lower in the newly diagnosed group, between-group differences were not statistically significant (**Figure 5F**).

3.6 Disease relapse and rescue therapy

No new LN relapses occurred in either group during follow-up. In the newly diagnosed group, one patient received rescue therapy with intravenous immunoglobulin at Month 20 because of a newly developed facial rash. In the relapsed group, three patients required rescue therapy. Two patients had worsening proteinuria and received CYC pulse therapy and multitarget therapy at Months 20 and 22, respectively. Another patient developed severe multisystem disease activity at Month 6 and was treated with telitacicept, intravenous immunoglobulin, continuous renal replacement therapy, and peritoneal dialysis, resulting in disease control. This patient subsequently discontinued BLM, was lost to follow-up, and ultimately progressed to ESKD.

3.7 Safety and Adverse Events

No BLM-related infusion reactions were observed, and infection rates were comparable between groups. Infections occurred in 10 patients (40.0%) in the newly diagnosed

group, and 6 patients (54.5%) in the relapsed group; upper respiratory tract infection and pneumonia were the most common events. No opportunistic or serious infections were observed. Hypogammaglobulinemia occurred in 9 patients in the newly diagnosed group and 3 in the relapsed group. The incidence of adverse events did not differ significantly between groups (**Table 3**).

4 Discussion

LN is one of the most severe organ manifestations of SLE and is a major contributor to ESKD and mortality. The main goals of LN management are early renal remission, relapse prevention, preservation of kidney function, and minimization of treatment-related toxicity [23]. However, even with conventional regimens, only approximately 60%-70% of pediatric patients achieve complete or partial remission, and relapse remains common after treatment tapering or withdrawal [22]. In recent years, growing evidence has highlighted the pivotal role of aberrant B-cell activation in the pathogenesis of SLE, spurring the development and clinical application of B-cell-targeted therapies. BLM, a monoclonal antibody targeting BAFF, was approved by the U.S. Food and Drug Administration for adult SLE in 2011; indications were subsequently expanded to cSLE and pediatric LN in 2019 and 2022, respectively. In China, BLM was approved by the National Medical Products Administration in 2020 for children aged 5 years and older with cSLE.

The BLISS-LN trial showed that adding BLM to standard therapy improves renal outcomes and reduces renal-related events in adults with LN. Pediatric studies have also reported favorable efficacy, but evidence in cLN remains limited [10,12,13]. To our knowledge, no previous study has specifically compared BLM outcomes between newly diagnosed and relapsed cLN. In this cohort, patients who received BLM during the newly diagnosed phase demonstrated higher rates of complete renal response and LLDAS achievement at 12 months, as well as more rapid reductions in disease activity and glucocorticoid exposure. However, after adjustment for baseline clinical characteristics, the association was most consistent for LLDAS attainment, whereas associations with renal response and DORIS remission were less robust. These findings suggest that the clinical context in which BLM is introduced may influence subsequent treatment trajectories, although they do not establish a causal benefit of earlier BLM initiation.

At 12 months, 94.7% of patients in the newly diagnosed group achieved CRR, consistent with findings reported by Gong et al. in newly diagnosed cLN patients [12]. This rate was higher than that in the relapsed group (55.6%), and the between-group difference emerged from Month 9 onward. Differences in the renal pathological state at BLM initiation offer one biologically plausible explanation for the heterogeneous renal responses [24]. Recurrent LN flares may be accompanied by cumulative structural injury, and higher chronicity indices have been associated with lower rates of proteinuria remission and CRR and with worse long-term renal outcomes [25,26]. In the available biopsy data from our cohort, glomerulosclerosis was recorded in 20.0%

of newly diagnosed patients and 45.5% of relapsed patients, while tubular atrophy was recorded in 0% and 36.4%, respectively; interstitial fibrosis was observed in 0% and 9.1%, respectively. The median NIH chronicity index was 0 (IQR 0–0) versus 1 (IQR 0–3), respectively (Supplementary Table 2). These descriptive patterns are compatible with greater chronic structural change in at least some relapsed patients. Therefore, the lower response observed in relapsed patients may reflect, at least partially, differences in disease reversibility rather than treatment timing alone.

The observed differences between newly diagnosed and relapsed patients may also reflect underlying differences in disease biology. Patients in the relapsed group had substantially longer disease duration and greater previous exposure to immunosuppressive therapies before BLM initiation. These features indicate that relapsed patients represented a population with a different therapeutic background and potentially greater cumulative disease burden.

Unlike conventional immunosuppression, which primarily targets broad immune activation, BLM selectively interferes with BAFF-mediated B-cell survival pathways. The clinical benefit of BLM may therefore depend on the relative contribution of active immune-mediated inflammation versus established structural injury at the time of treatment initiation. Patients with newly diagnosed disease may have a greater proportion of potentially reversible inflammatory lesions, whereas patients with relapsed disease may have accumulated chronic changes that are less amenable to immunomodulatory intervention.

Treat-to-target has become an important framework for SLE management. Sustained LLDAS or DORIS remission is associated with lower risks of organ damage accrual and severe flares [27]. In this study, the newly diagnosed group demonstrated higher hazards of achieving LLDAS and DORIS remission during follow-up. Furthermore, at 12 months, 73.7% and 36.8% of newly diagnosed patients achieved LLDAS and DORIS remission, respectively, consistent with findings from a recent multicenter Chinese cohort [28]. Given the limited sample size, these results should be interpreted as hypothesis-generating, but they suggest that disease status at BLM initiation may be relevant to achieving sustained disease control.

GCs remain essential for induction therapy, but cumulative exposure is strongly associated with growth impairment, infection, metabolic toxicity, and long-term organ damage in children. Therefore, current strategies emphasize rapid but safe GC tapering while maintaining disease control. In our study, both groups experienced substantial GC reduction after BLM initiation, but longitudinal analysis demonstrated a greater reduction trajectory in the newly diagnosed group. This observation may reflect more rapid control of inflammatory activity; however, differences in baseline disease characteristics and treatment history should also be considered. Future studies with larger cohorts are needed to determine whether BLM facilitates steroid-sparing strategies across different clinical contexts.

This study has limitations. First, the retrospective single-center design introduces potential selection bias and information bias. Second, the relapsed group differed from the newly diagnosed group in disease duration and prior treatment exposure before BLM initiation, which may have influenced subsequent outcomes. Third, the cohort was small, particularly at the 12-month assessment, resulting in wide confidence intervals and limiting multivariable adjustment. Finally, follow-up was relatively short for assessing kidney survival and late safety outcomes.

In conclusion, among children with cLN receiving BLM combined with standard therapy, disease status at BLM initiation was associated with differences in subsequent treatment trajectories. Patients treated during the newly diagnosed phase demonstrated more frequent achievement of treatment targets and greater improvement in disease activity measures. These findings suggest that the clinical context at the initiation of targeted B-cell therapy may influence therapeutic response. Prospective multicenter studies with larger sample sizes are required to determine how disease characteristics at BLM initiation influence long-term outcomes after BLM-based therapy.

5 Conflict of Interest

The authors declare that they have no competing interests.

6 Authors' contributions

WW: Software, Writing-original draft, Methodology, Investigation, Formal Analysis, Conceptualization, Data curation, Writing-review and editing. DW: Writing-original draft, Data curation, Conceptualization, Investigation, Writing-review and editing. YL: Methodology, Investigation, Software, Writing-review and editing, Formal Analysis. JL: Writing-review and editing, Investigation, Data curation. RZ: Data curation, Writing-review and editing, Investigation. NN: Writing-review and editing, Data curation, Investigation. CB: Writing-review and editing, Data curation, Investigation. SG: Writing-review and editing, Data curation, Investigation. QZ: Investigation, Software, Writing-review and editing, Methodology, Formal Analysis. HC: Writing-review and editing, Supervision, Conceptualization, Software, Investigation, Methodology, Formal Analysis, Resources, Funding acquisition, Project administration, Data curation, Validation.

7 Funding statement

Not applicable.

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9 Data Availability Statement

Data are available from the corresponding author upon reasonable request.

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Table 1 Baseline characteristics of the newly diagnosed and relapsed groups

Variable	Newly diagnosed group(n=25)	Relapse group(n=11)	Z/t/ χ^2	P value
Sex (male,n(%))	9(36%)	1(9.1%)		0.127
Age (years)	11.76 $\pm$ 1.81	14.0 $\pm$ 1.41	3.636	<0.001
Weight (kg)	46.18 $\pm$ 14.83	56.91 $\pm$ 11.49	-1.263	0.215
Height (cm)	155.76 $\pm$ 12.66	161.45 $\pm$ 11.97	-2.128	0.041
Disease duration(months)	0.77(0.53,1.17)	81.23(58.63,101.20)	4.726	<0.001
Renal pathology (n(%))				
II	3(12%)	1(9.1%)		1.000
III/IV	13(52%)	5(45.5%)		1.000
III/IV+V	8(32%)	4(36.4%)		1.000
V	1(4%)	1(9.1%)		0.524
Serum albumin(g/L)	26.71 $\pm$ 9.56	28.58 $\pm$ 9.72	-0.548	0.587
24-hour urinary protein(g)	1.9(0.615,4.83)	3.92(1.65,5.07)	1.563	0.124
>50mg/kg·d(n(%))	12(48%)	8(72.7%)		0.277
eGFR(mL/min/1.73 m ²)	100.77(31.405,119.95)	140.36(118.65,156.76)	2.988	0.002
AKI(n(%))	9(36%)	0		0.034
Immunological parameters(n(%))				
Low complement	23(92%)	9(81.8%)		0.570
Anti-dsDNA antibody Positive	21(84%)	8(72.7%)		0.650
Antinuclear antibodies Positive	25(100%)	11(100%)		
Anti-Sm antibody Positive	7(28%)	2(18.2%)		0.690
C3(g/L)	0.27(0.192,0.396)	0.512(0.38,0.82)	2.577	0.008
C4(g/L)	0.067(0.06,0.0705)	0.082(0.072,0.144)	2.96	0.003
SLEDAI-2K	18.28 $\pm$ 5.77	14.36 $\pm$ 3.85	2.05	0.048
Mild(5-9)	0	1(9.1%)		0.306
Moderate (10-14)	9(36%)	3(27.3%)		0.735
Severe ($\geq$ 15)	16(64%)	7(63.6%)		1.000
Systemic involvement (n(%))				
Fever	14(56%)	9(81.8%)		0.259
Serositis	12(48%)	5(45.5%)		1.000
Mucocutaneous	12(48%)	3(27.3%)		0.295
Haematological	20(80%)	6(54.5%)		0.224

Gastrointestinal	7(28%)	1(9.1%)		0.388
Respiratory	4(16%)	1(9.1%)		1.000
Neurological	4(16%)	1(9.1%)		1.000
Musculoskeletal	5(20%)	2(18.2%)		1.000
Treatment(n(%))				
Hydroxychloroquine	23(100%)	11(100%)		
Initial GC dose(mg)	60(60,60)	50(50,60)	-1.856	0.124
Immunosuppressive agents				0.828
CYC to MMF	7(28%)	3(27.3%)		
CYC to TAC	3(12%)	1(9.1%)		
MMF	7(28%)	5(45.5%)		
TAC	1(4%)	0		
Multitargeted therapy	7(28%)	2(18.2%)		
Methylprednisolone pulse therapy	17(68%)	4(36.4%)		0.141
Renal replacement therapy	6(24%)	0		0.148
ACE inhibitors	24(96%)	9(81.8%)		0.216

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; SLEDAI-2K, SLE Disease Activity 2000 Index; GC, glucocorticoid; CYC, cyclophosphamide; TAC, tacrolimus; MMF, mycophenolate mofetil.

Table 2 Primary and major secondary outcomes in the newly diagnosed and relapsed groups

Outcome	Newly diagnosed group(n=19)	Relapse group(n=9)	OR (95% CI)	P value
CRR at 12 months	18(94.7%)	5(55.60%)	14.40 (1.30-159.52)	0.026
PRR at 12 months	18(94.7%)	6(66.7%)	9.00 (0.78-103.73)	0.084
LLDAS at 12 months	14(73.7%)	2(22.2%)	9.80 (1.50-63.85)	0.017
DORIS at 12 months	7(36.8%)	1(11.1%)	4.67 (0.48-45.55)	0.214

CRR, complete renal response; DORIS, Definitions of Remission in SLE; LLDAS, lupus low disease activity state; PRR, partial renal response. P values were derived from Fisher exact tests. ORs and 95% CIs were calculated from 2 × 2 contingency tables.

Table 3 Adverse Events in the Newly Diagnosed and Relapsed Groups

Adverse Events (n (%))	Newly diagnosed group (n=25)	Relapsed Group(n=11)	P value
Infusion reaction	0	0	
Infection			0.483
Acute upper respiratory tract infection	6(24.0%)	3(27.3%)	

Bronchitis	1(4.0%)	0	
Pneumonia	3(12.0%)	1(9.1%)	
Urinary tract infection	0	2(18.2%)	0.087
Leukopenia	7(28.0%)	1(9.1%)	0.338
Hypogammaglobulinemia	9(36.0%)	3(27.3%)	0.715

Figure Legends

Figure 1. Flowchart of patient selection in this retrospective cohort study of childhood-onset lupus nephritis treated with belimumab.

Figure 2. Renal responses (CRR, PRR) and time-to-response analyses in newly diagnosed versus relapsed cLN after belimumab initiation. CRR, complete renal response; cLN, childhood-onset lupus nephritis; ND, newly diagnosed group; PRR, partial renal response; RL, relapse group. * $P < 0.05$, ** $P < 0.01$.

Figure 3. Treat-to-target outcomes (LLDAS and DORIS remission) and time-to-achievement in newly diagnosed versus relapsed cLN. cLN, childhood-onset lupus nephritis; DORIS, Definitions of Remission in SLE; LLDAS, lupus low disease activity state; ND, newly diagnosed group; RL, relapse group. * $P < 0.05$, ** $P < 0.01$.

Figure 4. Longitudinal changes in SLEDAI-2K scores and daily glucocorticoid dose following belimumab treatment in newly diagnosed versus relapsed cLN. cLN, childhood-onset lupus nephritis; GC, glucocorticoid; ND, newly diagnosed group; SLEDAI-2K, SLE Disease Activity 2000 Index; RL, relapse group. * $P < 0.05$, ** $P < 0.01$.

Figure 5. Longitudinal changes in proteinuria, serum albumin, complement (C3/C4), eGFR and IgG after belimumab initiation in newly diagnosed versus relapsed cLN. cLN, childhood-onset lupus nephritis; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; ND, newly diagnosed group; RL, relapse group. * $P < 0.05$, ** $P < 0.01$.

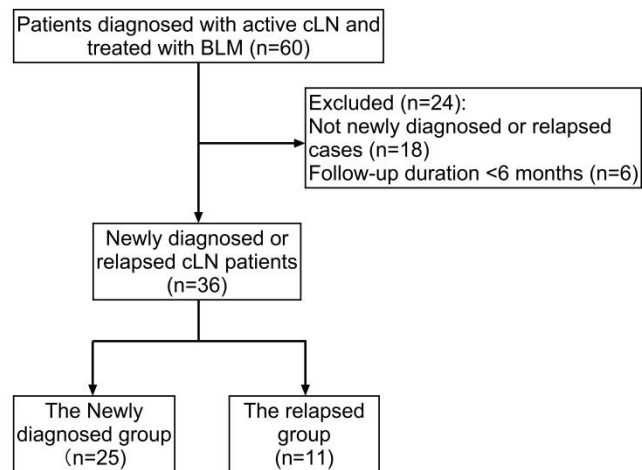


Figure 1 Flowchart of patient selection in this retrospective cohort study of childhood-onset lupus nephritis treated with belimumab.

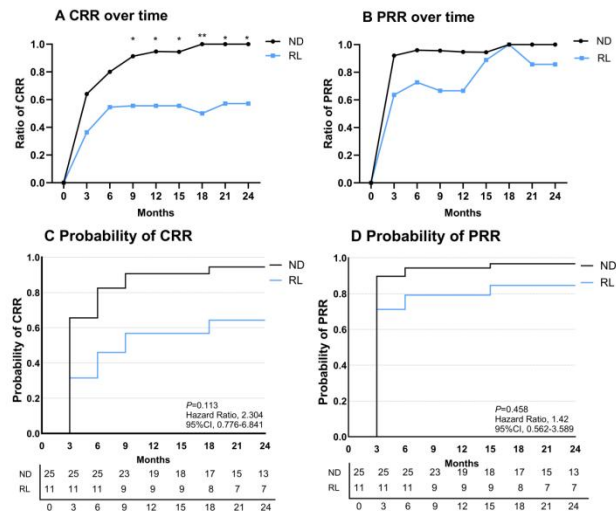


Figure 2 Renal responses (CRR, PRR) and time-to-response analyses in newly diagnosed versus relapsed cLN after belimumab initiation. CRR, complete renal response; cLN, childhood-onset lupus nephritis; ND, newly diagnosed group; PRR, partial renal response; RL, relapse group. * $p<0.05$, ** $p<0.01$.

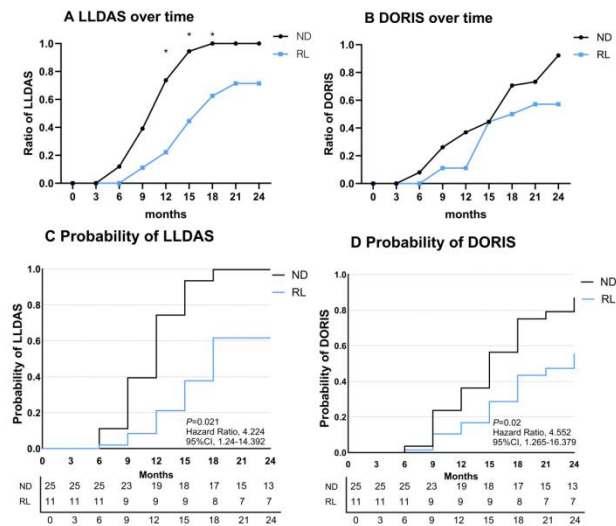


Figure 3 Treat-to-target outcomes (LLDAS and DORIS remission) and time-to-achievement in newly diagnosed versus relapsed cLN.cLN, childhood-onset lupus nephritis; DORIS, Definitions of Remission in SLE; LLDAS, lupus low disease activity state; ND, newly diagnosed group; RL, relapse group. * $p < 0.05$, ** $p < 0.01$.

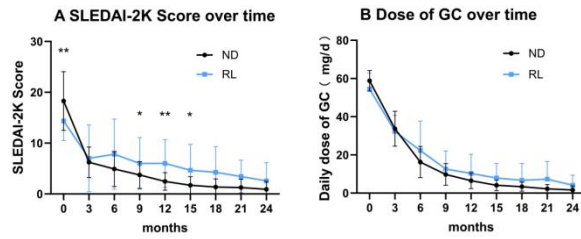


Figure 4 Longitudinal changes in SLEDAI-2K scores and daily glucocorticoid dose following belimumab treatment in newly diagnosed versus relapsed cLN. cLN, childhood-onset lupus nephritis; GC, glucocorticoid; ND, newly diagnosed group; SLEDAI-2K, SLE Disease Activity 2000 Index; RL, relapse group. * $p < 0.05$, ** $p < 0.01$.

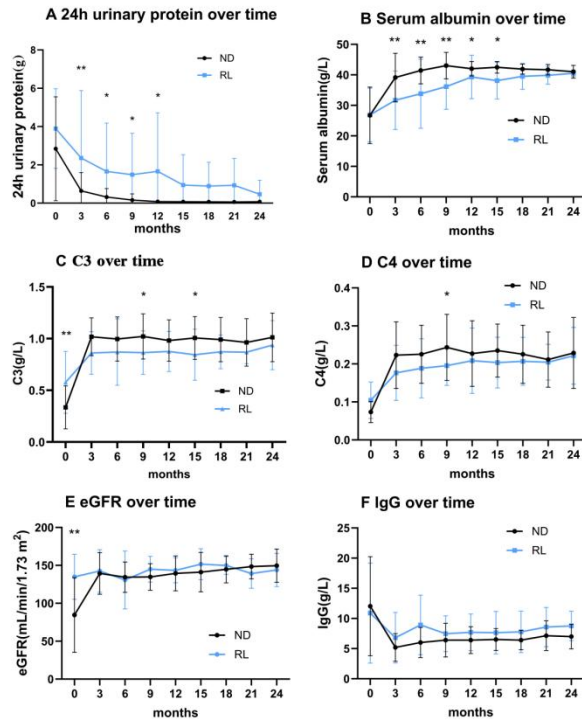


Figure 5 Longitudinal changes in proteinuria, serum albumin, complement (C3/C4), eGFR and IgG after belimumab initiation in newly diagnosed versus relapsed cLN. cLN, childhood-onset lupus nephritis; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; ND, newly diagnosed group; RL, relapse group. * $p < 0.05$, ** $p < 0.01$.

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