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*Original Article*

# Belimumab combined with mycophenolate mofetil for treating severe lupus nephritis: effects on renal recovery, immune regulation, and long-term prognosis

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**Abstract:** Objective: To assess the combined therapeutic effects of belimumab and mycophenolate mofetil (MMF) in severe lupus nephritis (LN), focusing on renal recovery, immune regulation, and long-term outcome. Methods: We retrospectively analyzed data from 188 patients hospitalized between March 2019 and April 2022. Of these, 106 received belimumab (10 mg/kg) in addition to standard therapy, while 82 received standard care alone. Endpoints included renal function indices (proteinuria, serum creatinine, albumin), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores, anti-dsDNA antibody titers, complement C3 and C4 levels, and inflammatory markers (hs-CRP, IL-6, TNF-α). Remission rates were calculated, and prognostic factors for end-stage renal disease (ESRD) and mortality were evaluated using Cox regression and competing risk analysis. Results: The combination therapy yielded a 94% remission rate, significantly higher than the 70% observed for controls (P<0.001). Complete remission was achieved in about 50% of treated patients, compared to 40% in the control group (P=0.025), with a notably lower non-responder rate. Belimumab-treated patients exhibited greater reductions in proteinuria, serum creatinine, SLEDAI score, erythrocyte sedimentation rate (ESR), and inflammatory cytokines, alongside increases in albumin and complement levels (all P<0.001). Baseline creatinine and albumin levels were consistent predictors of ESRD (P<0.001) and mortality (P=0.006) by multivariate and competing risk analyses. Conclusion: In severe LN, the combination of belimumab and MMF provided superior improvements in renal function, immune status, and long-term prognosis compared to standard therapy. Baseline renal biomarkers, particularly creatinine and albumin, may guide patient stratification and personalized treatment approaches.

**Keywords:** Belimumab, mycophenolate mofetil, lupus nephritis, clinical efficacy, systemic lupus erythematosus disease activity index, renal function

## Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease marked by impaired immune regulation and excessive activation of inflammatory pathways, leading to damage across multiple organ systems, particularly the kidneys [1]. Lupus nephritis (LN), a severe manifestation of SLE, affects 40-50% of patients and presents with various clinical signs, including proteinuria, hematuria, edema, hypertension, and impaired renal function [2, 3]. The extent of renal involvement correlates with overall disease activity and is a key prognostic factor. Severe LN can lead to irreversible kidney damage, progressing to end-stage renal disease (ESRD), which significantly worsens both lifespan and quality of life [4]. Thus, the primary therapeutic goals in severe LN are to restore kidney function, halt progression, and prevent irreversible loss of renal capacity.

Current treatment strategies for severe LN primarily involve glucocorticoids, immunosuppressive agents, and other immunomodulatory drugs [5]. While these therapies improve outcome and slow disease progression, their effectiveness is often limited, and prolonged use is

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associated with side effects such as increased infection risk, osteoporosis, and metabolic disorders like diabetes [6]. Furthermore, a subset of patients does not respond adequately to standard treatments, highlighting the need for new approaches that offer better efficacy with fewer side effects.

Belimumab, a recombinant humanized monoclonal antibody, is a targeted biological therapy for SLE [7]. It binds to and neutralizes B-cell activating factor (BAFF), reducing abnormal B cell activation, a key mechanism in SLE pathogenesis [8]. Its safety and efficacy have been established in various patient populations, resulting in global regulatory approval for SLE treatment [9]. Another key drug in LN therapy is mycophenolate mofetil (MMF), a potent immunosuppressant that inhibits T and B cell proliferation and antibody production, making it effective for both induction and maintenance therapy in severe LN [10-12]. However, some patients do not respond adequately to either therapy alone, providing a rationale for combining treatments to optimize outcome [13].

While the efficacy of belimumab in SLE is well-documented, evidence on its combination with MMF, specifically for severe LN, is limited [14]. Furthermore, systematic data on the effects of this combination on renal function, immune response, and long-term outcome are scarce. This study aims to fill this gap by evaluating the effects of belimumab plus MMF in severe LN, focusing on renal recovery, immunological markers, and prognosis over extended follow-up.

## Materials and Methods

### *Sample size calculation*

The required sample size was based on primary efficacy renal response rates reported by Yu et al. [15], with response incidences of 62% for the belimumab group and 37% for the placebo group. These values were used as expected response rates for the treatment (62%) and control (37%) cohorts. Using G*Power software for comparison of two independent proportions, we set a two-sided significance level (α) of 0.05 and statistical power (1 - β) of 90% (β=0.1). The calculation yielded a minimum of 78 participants per study arm. With a 1:1 allocation ratio, the total required sample size was 156 participants, sufficient to maintain the planned statistical power for all analyses.

### *Functional scoring*

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to quantify lupus disease activity. SLEDAI integrates 24 clinical and laboratory data across multiple organ systems (neurological, renal, dermatologic, musculoskeletal, hematologic, and immunologic), yielding a total score between 0 and 105. Higher scores reflect greater disease activity. SLEDAI values ≥12 is generally considered indicative of high disease activity, often correlating with multi-organ involvement and increased risk of irreversible organ damage. In LN, a SLEDAI ≥12 is used as a criterion for severe disease, and this threshold was applied to the inclusion criteria for patient enrollment [16].

### *General information*

This retrospective cohort study included 188 patients with severe LN (SLEDAI score ≥12 and pathologic classification of type III/IV) admitted between March 2019 and April 2022. Patients were divided into a combination therapy group (n=106) and a control group (n=82). The study was approved by the medical ethics committee of Tongchuan People's Hospital.

### *Inclusion and exclusion criteria*

Inclusion criteria: (1) Patients diagnosed with SLE according to the 2023 European Alliance of Associations for Rheumatology Updated Guidelines for SLE Management [17]; (2) Complete clinical data; (3) Renal biopsy confirmation with no contraindications to renal puncture; (4) Newly diagnosed patients in the active phase of LN; (5) Age ≥18 years.

Exclusion criteria: (1) Organ failure other than renal; (2) Coagulation disorders; (3) Infection with human immunodeficiency virus, tuberculosis, or hepatitis B virus; (4) Pregnancy.

### *Treatment regimens*

The control group received conventional therapy, including prednisone acetate tablets (National Pharmaceutical Group Rongsheng Pharmaceutical Co., Ltd.; H41020636; 5 mg/tablet) at 0.5-1.0 mg/kg body weight, adminis-

tered orally once daily; hydroxychloroquine sulfate tablets (Shanghai Shangsheng Pharmaceutical Co., Ltd.; H19990263; 0.1 g/tablet) at 0.2 g (2 tablets) twice daily orally; and MMF capsules (Qionglai Tianyin Pharmaceutical Co., Ltd.; H20080819; 0.25 g/capsule) at 0.75 g (3 capsules) twice daily orally. Treatment lasted for 6 months, with dosage adjustments based on patient condition and immunological markers to assess efficacy.

The combination group received the same conventional therapy, supplemented with belimumab (GlaxoSmithKline (Ireland) Limited; SJ20190032; 120 mg/vial) at 10 mg/kg body weight, administered by intravenous infusion. Belimumab was given every 2 weeks for the first 6 weeks, then every 4 weeks thereafter. Treatment duration was 6 months, with dosage adjustments and immunological monitoring identical to the control group.

*Clinical data collection*

At admission, clinical data were recorded, including demographic variables (age, gender, BMI), medical history (diabetes, hypertension), clinical and pathological classifications, and renal biopsy results (class III or IV). Histopathologic changes were described, including tubular atrophy, interstitial inflammatory cell infiltration, and fibrosis. Laboratory tests were performed before treatment and at the 6-month follow-up, assessing renal function (urinary total protein [UTP], serum creatinine [SCr], albumin [Alb]), disease activity (SLEDAI), ESR, immunological markers (anti-double-stranded DNA antibody [ds-DNA], complement components [C3, C4]), and inflammatory mediators (high-sensitivity C-reactive protein [Hs-CRP], interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α]).

*Laboratory testing methods*

Biochemical and immunological assessments were performed at baseline and after 6 months. Blood and urine samples were processed promptly. UTP, SCr, and Alb were quantified using a Beckman 5800 automated analyzer. Immunological indices (ds-DNA, C3, C4) were measured with a Siemens immunoassay analyzer. Inflammatory markers (hs-CRP, IL-6, TNF-α) were analyzed using enzyme-linked immunosorbent assay (ELISA, Shanghai Enzyme-linked Biotechnology Co., Ltd., China). Disease activity was assessed through SLEDAI scoring, and ESR was determined using the Westergren technique.

*Follow-up*

Patients were followed up through outpatient records, telephone interviews, and electronic medical records until March 2025. Follow-up occurred every 4 months in the first year and every 6 months thereafter. At each follow-up, clinical data, laboratory markers, adverse events, treatment efficacy, and health status were recorded. Composite endpoint events included all-cause mortality or progression to ESRD, with the endpoint defined as the first occurrence of either.

*Outcome measurements*

*Primary outcomes:* Comparison of clinical efficacy across treatment regimens and identification of independent prognostic factors for endpoint events.

*Secondary outcomes:* Assessment of changes in renal function, immune response, and inflammatory status pre- and post-treatment.

*Statistical analysis*

Data were analyzed using SPSS 27.0. Categorical variables were expressed as percentages and compared using the Chi-square test. Continuous variables were tested for normality with the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared using independent or paired t-tests; non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann-Whitney U test. Kaplan-Meier survival curves evaluated survival differences between groups, with comparisons made by the Log-rank test. Competing risk analysis assessed risk factors for endpoint events (ESRD, death). Time-dependent receiver operating characteristic (ROC) curve analysis, conducted with the "timeROC" package in R, evaluated the predictive performance of clinical variables for adverse outcomes at 1, 2, and 3 years, with the area under the curve (AUC) indicating discrimination ability. Correlation analyses used Pearson's coefficient for normally distributed

**Table 1.** Patient baseline characteristics

| Factor | Total | Combination Therapy Group (n=106) | Control Group (n=82) | Statistic | *P*-value |
|---|---|---|---|---|---|
| Age (years) | 33.72±10.09 | 33.80±9.85 | 33.61±10.44 | 0.129 | 0.897 |
| Gender | | | | 0.856 | 0.355 |
| Male | 155 (82.45%) | 85 (80.19%) | 70 (85.37%) | | |
| Female | 33 (17.55%) | 21 (19.81%) | 12 (14.63%) | | |
| BMI (kg/m$^2$) | 23.21±1.41 | 23.11±1.40 | 23.35±1.42 | -1.178 | 0.240 |
| Diabetes | | | | 1.183 | 0.277 |
| Yes | 24 (12.77%) | 16 (15.09%) | 8 (9.76%) | | |
| No | 164 (87.23%) | 90 (84.91%) | 74 (90.24%) | | |
| Hypertension | | | | 1.088 | 0.297 |
| Yes | 16 (8.51%) | 11 (10.38%) | 5 (6.10%) | | |
| No | 172 (91.49%) | 95 (89.62%) | 77 (93.90%) | | |
| Clinical Classification | | | | 0.564 | 0.453 |
| Nephrotic Syndrome | 118 (62.77%) | 69 (65.09%) | 49 (59.76%) | | |
| Acute Nephritis | 70 (37.23%) | 37 (34.91%) | 33 (40.24%) | | |
| Pathological Classification | | | | 0.308 | 0.579 |
| III | 115 (61.17%) | 63 (59.43%) | 52 (63.41%) | | |
| IV | 73 (38.83%) | 43 (40.57%) | 30 (36.59%) | | |
| Tubular Atrophy | | | | 0.527 | 0.913 |
| None | 29 (15.43%) | 16 (15.09%) | 13 (15.85%) | | |
| Focal | 34 (18.09%) | 18 (16.98%) | 16 (19.51%) | | |
| Multifocal | 65 (34.57%) | 36 (33.96%) | 29 (35.37%) | | |
| Diffuse | 60 (31.91%) | 36(33.96%) | 24 (29.27%) | | |
| Interstitial Inflammatory Cell Infiltration | | | | 1.055 | 0.788 |
| None | 18 (9.57%) | 9 (8.49%) | 9 (10.98%) | | |
| Focal | 23 (12.23%) | 12 (11.32%) | 11 (13.41%) | | |
| Multifocal | 71 (37.77%) | 39 (36.79%) | 32 (39.02%) | | |
| Diffuse | 76 (40.43%) | 46 (43.40%) | 30 (36.59%) | | |
| Interstitial Fibrosis | | | | 1.306 | 0.728 |
| None | 14 (7.45%) | 7 (6.60%) | 7 (8.54%) | | |
| Focal | 26 (13.83%) | 13 (12.26%) | 13 (15.85%) | | |
| Multifocal | 62 (32.98%) | 34 (32.08%) | 28 (34.15%) | | |
| Diffuse | 86 (45.74%) | 52 (49.06%) | 34 (41.46%) | | |

Note: BMI = Body Mass Index.

variables and Spearman's coefficient for non-normally distributed variables. All tests were two-sided, with significance set at P<0.05.

## Results

*Comparison of baseline characteristics*

Baseline characteristics, including age, gender, BMI, diabetes, hypertension, clinical classification, pathological classification, tubular atrophy, interstitial inflammatory cell infiltration, and interstitial fibrosis showed no significant differences between the groups (all P>0.05, **Table 1**).

*Comparison of clinical efficacy*

The combination therapy group achieved a significantly higher total remission rate compared to the control group (94.23% vs. 70.49%, P<0.001). Specifically, the combination group had a complete remission rate of 50.00%, compared to 40.24% for the control group (P= 0.025), and a partial remission rate of 46.23% versus 40.24%. The non-remission rate was

**Table 2.** Comparison of efficacy evaluation in treatment of severe lupus nephritis

| Group | Combination Therapy Group (n=106) | Control Group (n=82) | $X^2$/Z | *P*-value |
|---|---|---|---|---|
| Complete Remission | 53 (50.00%) | 33 (40.24%) | 2.238 | 0.025 |
| Partial Remission | 49 (46.23%) | 33 (40.24%) | | |
| No Remission | 4 (3.77%) | 16 (19.51%) | | |
| Total Remission Rate (%) | 102 (96.23%) | 66 (80.49%) | - | <0.001 |

Note: Chi-square test using Fisher's exact test.

**Table 3.** Comparison of changes in renal function-related indicators before and after treatment in both groups (UTP, SCr, Alb)

| Group | | Combination Therapy Group (n=106) | Control Group (n=82) | t/Z | *P*-value |
|---|---|---|---|---|---|
| UTP (g/24 h) | Before Treatment | 4.90 (1.47) | 4.85 (1.30) | 0.368 | 0.713 |
| | After Treatment | 1.30 (0.30)* | 2.20 (0.40)* | 11.687 | <0.001 |
| SCr (μmol/L) | Before Treatment | 159.64±28.06 | 157.29±25.61 | 0.591 | 0.555 |
| | After Treatment | 73.47±15.84* | 93.98±17.50* | -8.406 | <0.001 |
| Alb (g/L) | Before Treatment | 23.00±2.76 | 23.66±3.00 | -1.579 | 0.116 |
| | After Treatment | 33.07±3.72* | 29.80±2.71* | 6.711 | <0.001 |

Note: *P<0.05 compared to pretreatment; UTP = Urinary Total Protein, SCr = Serum Creatinine, Alb = Albumin.

**Table 4.** Comparison of changes in SLEDAI scores and ESR before and after treatment in both groups

| Group | | Combination Therapy Group (n=106) | Control Group (n=82) | t/Z | *P*-value |
|---|---|---|---|---|---|
| SLEDAI Score | Before Treatment | 17.00 (5.00) | 17.00 (5.75) | 0.172 | 0.863 |
| | After Treatment | 7.00 (4.00)* | 9.00 (2.00)* | 5.289 | <0.001 |
| ESR (mm/h) | Before Treatment | 59.20±12.46 | 59.80±13.54 | -0.319 | 0.75 |
| | After Treatment | 29.33±8.51* | 39.20±9.42* | -7.523 | <0.001 |

Note: *P<0.05 compared to pretreatment; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, ESR = Erythrocyte Sedimentation Rate.

significantly lower for the combination group (3.77% vs. 19.51%, P<0.001) (**Table 2**).

*Comparison of renal function markers*

The combination therapy group demonstrated greater improvements in UTP, SCr, and Alb (all P<0.001). Intra-group differences were significant for UTP and Alb in both groups (both P<0.001). However, inter-group differences in UTP (P=0.713) and SCr (P=0.555) before and after treatment were not significant, although the combination group showed superior overall improvement (**Table 3**).

*Comparison of SLEDAI scores and ESR*

Both groups exhibited significant reductions in SLEDAI scores and ESR post-treatment (both P<0.001). The combination therapy group showed greater improvements in SLEDAI scores and ESR, although inter-group differences were not statistically significant (P=0.863 for SLEDAI, P=0.75 for ESR) (**Table 4**).

*Comparison of immunological markers*

Both groups showed significant improvements in ds-DNA, C3, and C4 levels post-treatment (all P<0.001). The combination therapy group demonstrated more pronounced improvements in C3 and C4 (both P<0.001). Inter-group differences in ds-DNA were not significant (P=0.992), but overall improvements in immunological markers were greater in the combination group (**Table 5**).

*Comparison of inflammatory markers*

Both groups showed significant reductions in inflammatory markers (hs-CRP, IL-6, and TNF-α) - post-treatment (all P<0.001). The combination

**Table 5.** Comparison of changes in ds-DNA, C3, and C4 before and after treatment in both groups

| Group | | Combination Therapy Group (n=106) | Control Group (n=82) | t/Z | *P*-value |
|---|---|---|---|---|---|
| ds-DNA (IU/L) | Before Treatment | 39.49±5.63 | 39.49±6.33 | 0.01 | 0.992 |
| | After Treatment | 18.98±3.20* | 26.62±4.31* | -13.947 | <0.001 |
| C3 (g/L) | Before Treatment | 0.37±0.11 | 0.38±0.11 | -0.623 | 0.534 |
| | After Treatment | 0.58±0.10* | 0.51±0.11* | 4.464 | <0.001 |
| C4 (g/L) | Before Treatment | 0.08 (0.03) | 0.08 (0.03) | 1.198 | 0.231 |
| | After Treatment | 0.15 (0.06)* | 0.11 (0.04)* | 5.354 | <0.001 |

Note: *P<0.05 compared to pretreatment; ds-DNA = Double-Stranded DNA, C3 = Complement 3, C4 = Complement 4.

**Table 6.** Comparison of changes in inflammatory factors before and after treatment in both groups

| Group | | Combination Therapy Group (n=106) | Control Group (n=82) | t/Z | *P*-value |
|---|---|---|---|---|---|
| Hs-CRP (mg/mL) | Before Treatment | 40.41±5.91 | 40.79±6.55 | -0.42 | 0.675 |
| | After Treatment | 15.29±2.73* | 18.56±3.40* | -7.322 | <0.001 |
| IL-6 (ng/mL) | Before Treatment | 80.95 (10.57) | 80.35 (9.15) | 0.104 | 0.917 |
| | After Treatment | 44.91±5.12* | 49.61±4.18* | -6.762 | <0.001 |
| TNF-α (ng/mL) | Before Treatment | 108.13±10.32 | 105.76±11.52 | 1.485 | 0.139 |
| | After Treatment | 53.24±6.13* | 61.69±6.11* | -9.376 | <0.001 |

Note: *P<0.05 compared to pretreatment; Hs-CRP = High-Sensitivity C-Reactive Protein, IL-6 = Interleukin 6, TNF-α = Tumor Necrosis Factor Alpha.

therapy group showed significant intra-group reductions in all markers (P<0.001). Inter-group differences were significant for IL-6 (P<0.001), but not for Hs-CRP (P=0.675) or TNF-α (P=0.139). Overall, the combination group exhibited superior reductions in inflammatory markers (**Table 6**).

*Association between clinical variables and prognosis*

Correlation analysis showed that pre-treatment serum creatinine (SCr) (r=0.290, P<0.001), SLEDAI score (r=0.236, P=0.001), clinical classification (r=0.215, P=0.003), albumin (Alb) (r=0.185, P=0.011), and treatment regimen (r=-0.172, P=0.019) were weakly associated with prognosis. Higher SCr, SLEDAI score, and more severe clinical classification were associated with worse outcome, while lower Alb levels were linked to poorer prognosis. The treatment regimen showed a weak negative correlation, suggesting a possible protective effect. No significant associations were observed with the following variables: tubular atrophy (r=-0.115, P=0.116), pre-treatment ESR (r=-0.109, P=0.138), age (r=-0.089, P=0.227), hypertension (r=-0.084, P=0.253), pre-treatment C3 (r=0.079, P=0.282), pre-treatment C4 (r=-0.076, P=0.297), pre-treatment TNF-α (r=0.064, P=0.381), pre-treatment IL-6 (r=0.058, P=0.429), pre-treatment ds-DNA (r=-0.053, P=0.473), BMI (r=-0.045, P=0.543), pre-treatment UTP (r=0.032, P=0.664), gender (r=-0.023, P=0.751), interstitial inflammatory cell infiltration (r=-0.016, P=0.824), interstitial fibrosis (r=0.011, P=0.880), pre-treatment Hs-CRP (r=-0.009, P=0.898), pathological classification (r=0.007, P=0.928), and diabetes (r=-0.006, P=0.936) (**Figure 1**).

*Prognostic differences by Kaplan-Meier survival analysis*

Kaplan-Meier survival analysis showed that the combination therapy group had a significantly lower risk of adverse outcome compared to the control group (P=0.017, **Figure 2A**). Patients with acute nephritis had a higher risk of poor outcome than those with nephrotic syndrome (P=0.004, **Figure 2B**). Pre-treatment SCr (P<0.001, **Figure 2C**), pre-treatment Alb (P=0.004, **Figure 2D**), and pre-treatment SLEDAI score >15 (P<0.001, **Figure 2E**) were significantly associated with worse prognosis.

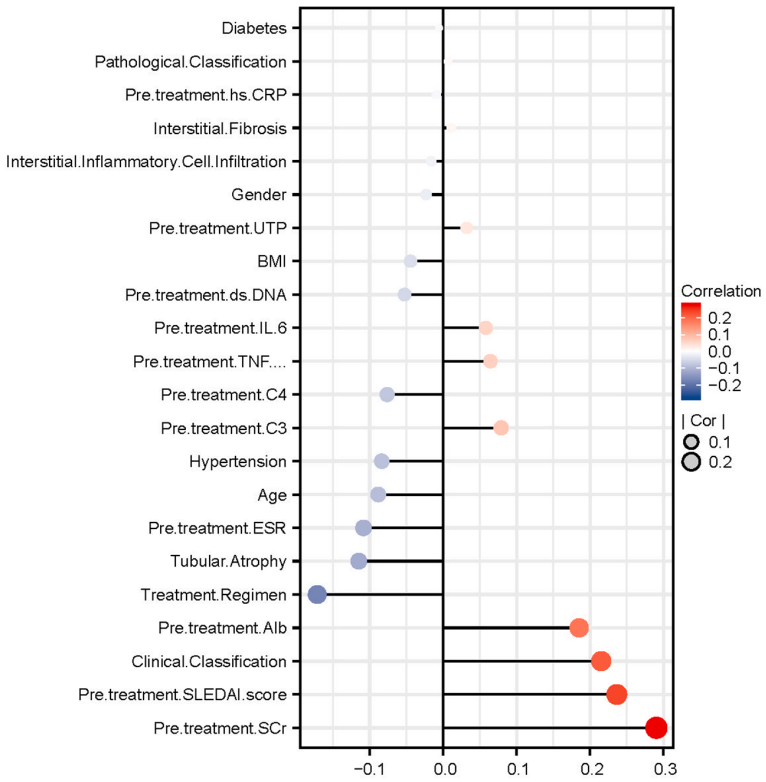


**Figure 1.** Correlation analysis of clinical variables and patient prognosis.

*Temporal predictive performance of clinical variables*

Time-dependent ROC analysis evaluated the prognostic performance of key clinical variables at 1, 2, and 3 years. The treatment regimen (**Figure 3A**) showed increasing predictive power over time (AUCs: 0.681, 0.683, 0.692). Pre-treatment SCr (**Figure 3C**) exhibited the highest predictive performance (AUC=0.757 at year 3). Pre-treatment Alb (**Figure 3D**) had limited predictive value initially but reached an AUC of 0.689 by year 3. Clinical classification (**Figure 3B**) showed poor prognostic discrimination (AUCs ~0.5). Pre-treatment SLEDAI score (**Figure 3E**) had consistently low AUCs (<0.6), indicating limited prognostic value. Treatment regimen and pre-treatment SCr were the most reliable predictors of adverse outcome, particularly at year 3.

## Discussion

This study evaluated the clinical efficacy of belimumab combined with MMF in treating severe LN, focusing on its effects on renal function, immune response, and long-term prognosis. SLE is a chronic autoimmune disease, with LN being a frequent and severe complication. While conventional treatments alleviate symptoms, they are associated with significant adverse effects, and some patients show suboptimal responses. Belimumab, a recombinant humanized monoclonal antibody, inhibits BAFF, thereby reducing autoimmune activity. When combined with MMF, a potent immunosuppressive agent, this regimen enhances immune modulation. By assessing clinical outcomes, renal function, and immunological markers, this study provides evidence for a novel therapeutic strategy for severe LN, offering a promising option for affected patients.

Our results demonstrate that belimumab combined with MMF significantly improves clinical outcomes in severe LN. The combination therapy group showed a markedly higher overall remission rate than the control group, with increases in both complete remission and partial remission. Conversely, the proportion of patients without remission was significantly reduced for the combination group (3.77% vs. 19.51%, P<0.001), highlighting a clear therapeutic advantage. These findings are consistent with the phase 2 proof-of-concept study by Kraaij et al. [18], in which combined B-cell targeted therapy with rituximab and belimumab achieved substantial renal responses in patients with severe, refractory LN. Similarly, Gatto et al. [19] in a multicenter real-world analysis found that the addition of belimumab resulted in primary and complete renal responses in most LN patients, further supporting our findings and reinforcing belimumab's role as an effective adjunct in LN management.

Regarding renal function, patients receiving the combined regimen showed significant post-treatment improvements in UTP, SCr, and Alb levels. Similar trends were observed by Sumichika et al. [20], who reported reductions in both SLEDAI scores and glucocorticoid

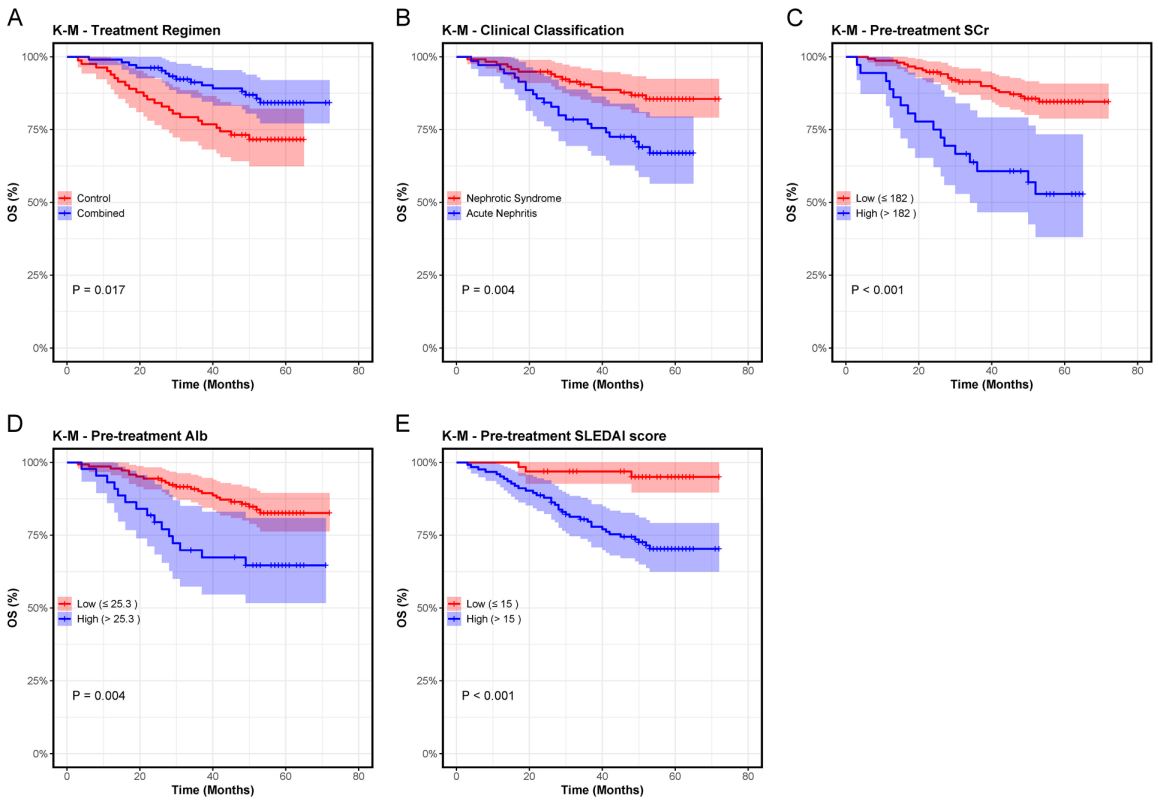


**Figure 2.** Kaplan-Meier survival curves for combination therapy group and control group under different clinical classifications, tubular atrophy types, and pre-treatment indicators. A. Treatment Regimen: Kaplan-Meier curves for OS between the combination therapy group and control group, with the combination therapy group having longer survival. B. Clinical Classification: Kaplan-Meier curves for OS between patients with nephrotic syndrome and acute nephritis, with acute nephritis patients having shorter survival. C. Pre-treatment SCr: Kaplan-Meier curves for OS between patients with lower and higher pre-treatment serum creatinine (SCr) levels, with lower SCr levels associated with longer survival. D. Pre-treatment Alb: Kaplan-Meier curves for OS between patients with lower and higher pre-treatment albumin (Alb) levels, with higher Alb levels associated with longer survival. E. Pre-treatment SLEDAI Score: Kaplan-Meier curves for OS between patients with lower and higher pre-treatment SLEDAI scores, with lower SLEDAI scores associated with longer survival. Note: SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SCr = Serum Creatinine, Alb = Albumin.

requirements in SLE patients treated with belimumab. In our study, the combination group also showed significant declines in SLEDAI scores and ESR, suggesting effective suppression of disease activity. The enhanced therapeutic effect likely reflects complementary mechanisms of action: belimumab reduces B cell activation by binding BAFF, while MMF suppresses purine synthesis, limiting T- and B-cell proliferation [21, 22].

In immunological assessments, anti-dsDNA antibodies, complement C3, and C4 improved significantly in the combination group. Inflammatory markers, including Hs-CRP, IL-6, and TNF-α, also showed reductions. Stohl et al. [23] provided mechanistic insight, showing that prolonged belimumab therapy depletes specific B cell subsets and lowers serum IgG levels. Elevated baseline B cell counts predicted better systemic lupus response index-4 outcomes, while higher plasma cell levels were linked to poorer responses. This suggests that belimumab selectively depletes autoantibody-producing plasma cells, consistent with the immunological changes observed in our study. Parodis et al. [24] also noted that early post-treatment changes in B and plasma cell kinetics could predict disease relapse, with transient B cell expansion followed by memory B cell decline marking sustained remission.

Compared to controls, the combination therapy group exhibited superior results across remission rates, renal indices, and immunological profiles, with larger magnitudes of change in each index. Depascale et al. [25] emphasized that early initiation of belimumab enhances its

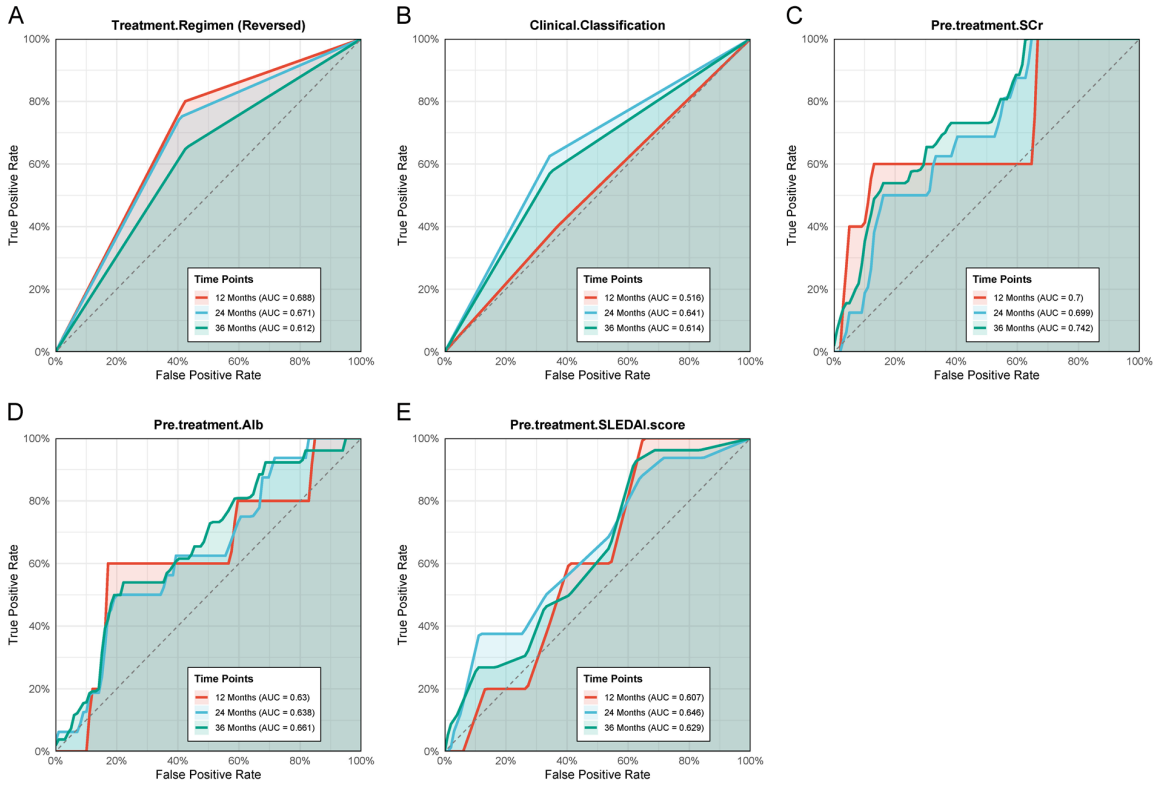


**Figure 3.** Time-dependent ROC curves of relevant factors for predicting prognosis in patients. A. ROC curves of Treatment Regimen for predicting poor prognosis at 1, 2, and 3 years in patients. B. ROC curves of Clinical Classification for predicting poor prognosis at 1, 2, and 3 years in patients. C. ROC curves of Pre-treatment SCr for predicting poor prognosis at 1, 2, and 3 years in patients. D. ROC curves of Pre-treatment Alb for predicting poor prognosis at 1, 2, and 3 years in patients. E. ROC curves of Pre-treatment SLEDAI score for predicting poor prognosis at 1, 2, and 3 years in patients.

clinical effect, a principle reflected in our study design. However, they also highlighted unresolved issues such as optimal discontinuation timing and the potential role of combining belimumab with other biologics, suggesting areas for future research. Our findings provide strong evidence that pairing belimumab with MMF may exceed the efficacy of monotherapy. Plüß et al. [8] expanded on belimumab's molecular mechanism as a fully human IgG1λ monoclonal antibody capable of neutralizing soluble BAFF, a feature that likely strengthens its role in LN therapy.

Correlation and time-dependent ROC curve analyses revealed that pre-treatment SCr and Alb levels were significant predictors of long-term prognosis. These findings are consistent with Gatto et al. [19], who showed that lower baseline creatinine levels predicted better renal responses to belimumab. Liu et al. [26] demonstrated belimumab's efficacy in severe LN patients requiring dialysis, with most achieving increased urine output and reduced SCr. Ding et al. [27] found that urinary Alb levels were independently associated with histologic severity in LN, indicating Alb's role as an early marker of renal injury. Nie et al. [28] noted that hypoalbuminemia was linked to serositis in LN, a marker of SLE activity and worse prognosis. Collectively, these studies underscore pre-treatment SCr and Alb as critical prognostic indicators, reflecting the extent and reversibility of renal damage.

Notably, Liu et al. [26] observed belimumab's effectiveness in dialysis-dependent LN patients, with most discontinuing dialysis and showing reduced SCr levels. This suggests belimumab holds potential for treating severe cases, thereby broadening its therapeutic applicability. Atisha-Fregoso et al. [7] investigated the use of belimumab following rituximab and cyclophosphamide in LN, reporting no significant improvement in clinical efficacy but noting sustained reductions in B-cell levels and

enhanced negative selection of autoreactive B cells. These immunologic effects align with our findings, reinforcing belimumab's role in immune regulation.

Despite its contributions, this study has limitations. As a retrospective cohort study, it was subject to selection and recall biases, which may limit the generalizability of the findings. The follow-up duration of 1 year was relatively short, limiting the ability to assess long-term prognosis fully. Although combination therapy significantly improved short-term outcomes, its long-term effects require extended follow-up. Additionally, the sample size was modest, which may have limited the detection of subtle differences between groups.

Future research should focus on large-scale multicenter randomized controlled trials to validate the long-term efficacy of belimumab combined with MMF, particularly in patients with type III and IV LN pathological classifications. Extended follow-up is needed to assess the regimen's impact on renal protection and ESRD prevention, ensuring its long-term safety and efficacy.

## Conclusion

Belimumab combined with MMF significantly enhanced clinical outcomes in severe LN, with notable improvements in remission rate, renal function, immune response, and inflammatory markers. This combination therapy offers a promising strategy for managing severe LN, particularly for improving short-term clinical efficacy and supporting renal protection.

## Disclosure of conflict of interest

None.

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