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Original Article

ORIGINAL ARTICLE

Oral glucocorticoids with intravenous cyclophosphamide or oral glucocorticoids alone in the treatment of IgA nephropathy present with nephrotic syndrome and mesangioproliferative glomerulonephritis

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ABSTRACT

Background. Few studies have evaluated the treatment of immunoglobulin A nephropathy (IgAN) patients with nephrotic syndrome (NS) and mesangioproliferative glomerulonephritis (MPGN). The aim of this study was to compare the therapeutic effects of oral glucocorticoids (GCS) combined with intravenous cyclophosphamide (CTX) and oral GCS alone in the treatment of the MPGN-IgAN patients with NS.

Methods. Biopsy-proven primary IgAN patients who were aged ≥14 years at diagnosis, had coexistent NS and MPGN and estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2, and were treated by oral GCS combined with intravenous CTX or oral GCS alone for 6–12 months were retrospectively included. The patients in the GCS + CTX (prednisone 0.6–0.8 mg/kg/day and intravenous CTX 0.6–1.0 g monthly) or GCS (prednisone 0.8–1 mg/kg/day) group were rather matched at a 1:1 ratio on key characteristics by propensity score matching. The primary outcome was defined as either complete remission or partial remission at Month 24. The secondary outcome was a composite renal endpoint defined as a 50% decline in eGFR, doubling of serum creatinine or progression to end-stage kidney disease.

Results. Among the 146 IgAN patients who met the inclusion criteria, 42 patients were enrolled in the GCS + CTX group, and 42 patients were enrolled in the GCS group after propensity score matching. The clinical and histological parameters were similar between the two groups. Remission occurred more frequently in the GCS + CTX group at Month 6 (88.1% vs 52.4%, $P < 0.001$), Month 12 (88.1% vs 56.1%, $P = 0.001$) and Month 24 (85.0% vs 47.5%, $P < 0.001$) than in the GCS group. Moreover, subgroup analysis revealed that the higher response rate at Month 24 in the GCS + CTX group than in the GCS group was also present in different subgroups defined by sex, age, eGFR or Oxford MEST-C. Notably, we found that eGFR decreased at a lower rate in patients from the GCS + CTX group than in patients from the GCS group [eGFR slope: 0.05

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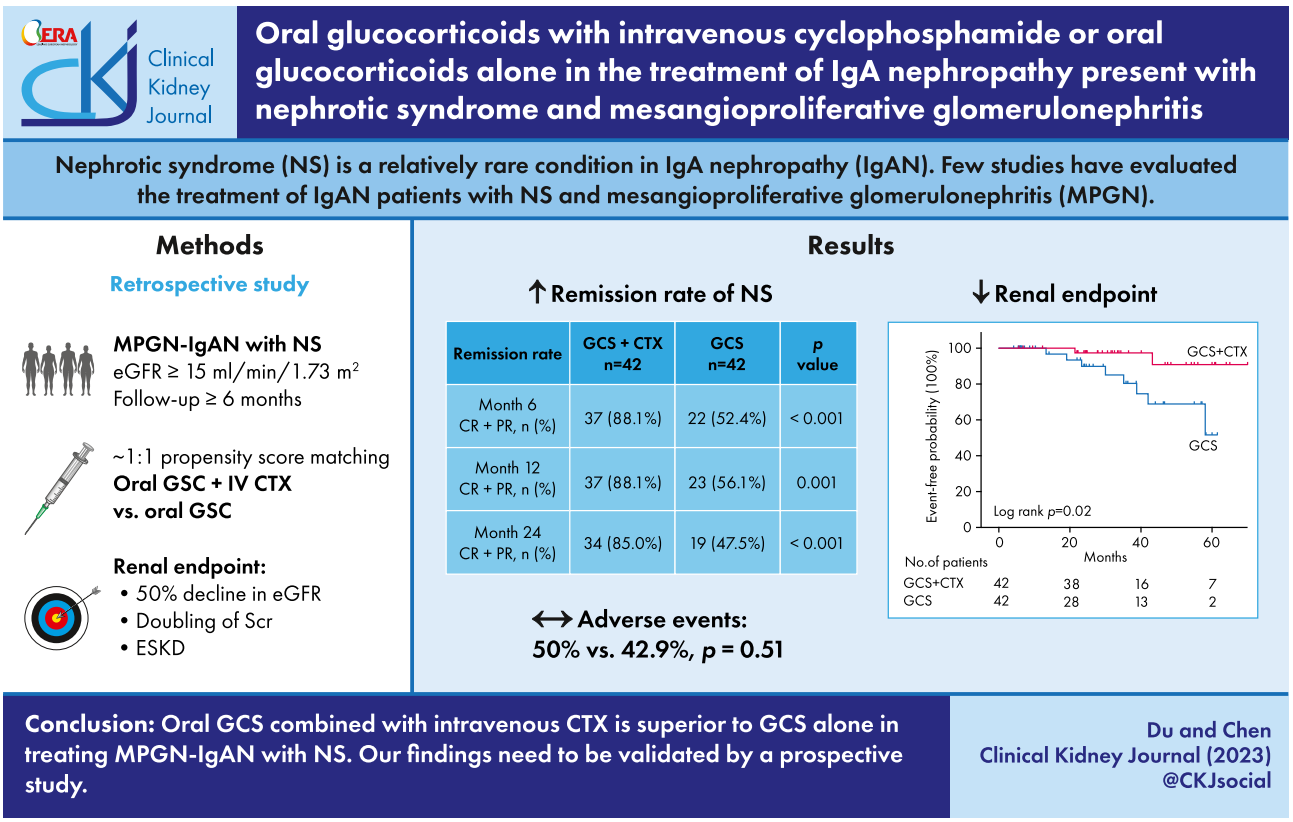
(–3.09, 3.67) vs –2.56 (–11.30, 0.86) mL/min/1.73 m^2/year, $P = 0.03$]. Based on multivariate Cox regression analysis, GCS + CTX treatment was found to be independently associated with a decrease in risk for the composite endpoint after adjusted by the International Risk Prediction Score with race (hazard ratio = 0.17, 95% confidence interval 0.04–0.83, $P = .03$). There was no significant difference in adverse events (50.0% vs 42.9%, $P = 0.51$) or serious adverse events (7.1% vs 11.9%, $P = .71$) between the two groups.

Conclusions. Oral GCS combined with intravenous CTX is superior to GCS alone in treating MPGN-IgAN patients combined with NS. As the retrospective design and small sample size, our findings need to be validated by a prospective study.

LAY SUMMARY

Immunoglobulin A nephropathy (IgAN) is the leading cause of end-stage renal disease in youth worldwide. Nephrotic syndrome (NS) is a relatively rare condition in IgAN patients, accounting for approximately 5%–15% of all IgAN patients. There are two common pathological types of IgAN with NS, minimal-change disease (MCD-IgAN) and mesangioproliferative glomerulonephritis (MPGN-IgAN). The former has been shown to respond well to glucocorticoids (GCS) and is suggested to be treated as MCD based on the 2021 KDIGO guidelines. However, the treatment strategy for the latter is not clear since there have been few studies discussing treatment options for MPGN-IgAN patients. This is the first study to compare the efficacy and safety of GCS combined with cyclophosphamide (CTX) versus GCS alone for the treatment in patients with MPGN-IgAN combined with NS. We found that the combination of GCS and CTX was more effective in reducing urinary protein than GCS alone. Furthermore, we determined that GCS combined with CTX was associated with a reduced risk of renal function deterioration in the treatment of MPGN-IgAN patients with NS. Finally, we found there was no significant difference of adverse events between the two treatment groups. In conclusion, oral GCS combined with intravenous CTX is superior to GCS alone in treating MPGN-IgAN patients combined with NS. Our study provides important evidence for the treatment of IgAN patients with NS and MPGN.

GRAPHICAL ABSTRACT



Keywords: cyclophosphamide, glucocorticoids, IgA nephropathy, nephrotic syndrome, prognosis

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common type of primary glomerulonephritis and a leading cause of end-stage kidney disease (ESKD) in youth worldwide. Approximately 15%–40% of IgAN patients develop ESKD gradually and require renal replacement therapy within 20 years of disease onset [1, 2]. Clinical and histological manifestations of IgAN are highly diverse. Asymptomatic urine abnormalities are the most common clinical manifestation, followed by transient gross hematuria (usually after upper respiratory or other types of mucosal infection) and varying degrees of proteinuria, but nephrotic syndrome (NS) is rarely observed. Renal pathology in IgAN patients is characterized by mesangial cell proliferation and mesangial matrix hyperplasia; however, other renal injuries, including lesions of the glomerulus, tubulointerstitium or small blood vessels, may also be observed. The pathogenesis of IgAN remains largely unknown, and recent studies indicate that excessive production of galactose-deficient IgA1 (Gd-IgA1) is crucially involved in the disease. There is increasing evidence that Gd-IgA1-producing cells predominantly originate from Peyer's patches of gut-associated lymphoid tissues (GALTs) [3, 4]. This finding is further supported by the study that showed that budesonide (Nefecon), a slow-release medication that targets the terminus of the ileum, has been demonstrated to have a proteinuria-reducing effect on IgAN patients with a high risk of progression [5].

NS is a relatively rare condition in IgAN, and occurs in approximately 5%–15% of all IgAN patients [6–9]. There are two common pathological types of IgAN that occur in patients with NS. The first is minimal-change disease (MCD-IgAN), which has been shown to respond well to glucocorticoids (GCS) and has a relatively favorable prognosis [10–12]. According to the 2021 KDIGO guidelines, MCD-IgAN should be treated as MCD [13]. The other pathological type is mesangioproliferative glomerulonephritis (MPGN-IgAN), in which patients typically have a lower estimated glomerular filtration rate (eGFR), more acute lesions and worse kidney prognosis unless the resolution of proteinuria is achieved. In an observational study of 1165 MPGN-IgAN patients [171 (14.7%) with NS], the 5-year renal survival rate in the NS group (73.1%) was significantly lower than that in the non-NS group (87.8%) ($P < .001$), indicating that NS was a predictor of poor renal outcome in MPGN-IgAN patients [6].

Few studies have described treatment options for MPGN-IgAN patients presenting with NS, and most are based on limited patient numbers. These studies revealed that GCS therapy is less effective in patients with MPGN-IgAN than in patients with MCD-IgAN [14, 15]. In addition, well-designed randomized clinical trials, such as the TESTING (Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy) or STOP-IgAN (Supportive versus immunosuppressive therapy for the treatment of progressive IgA nephropathy) studies, did not focus on the treatment of IgAN patients with NS or exclude these patients from study recruitment, resulting in a lack of evidence on how to treat these patients [16, 17]. GCS therapy achieved remission rates of approximately 50%–90% for MPGN-IgAN patients with NS based on previous studies [6–8]. Rasić *et al.* [18] enrolled 19 MPGN-IgAN patients with NS and observed that five of six (83.3%) patients treated with oral GCS combined with intravenous cyclophosphamide (CTX) achieved complete remission (CR) or partial remission (PR). Moreover, seven of eight (87.5%) patients treated with oral GCS alone attained CR or PR, and the remission rates were similar between the two groups. However, the sample size of the study was very small, and the clinical characteristics of patients at baseline and the time to remission were unknown.

Based on very limited evidence, patients with MPGN-IgAN are suggested to be managed in the same way as patients at high risk of progressive IgAN [13]. In this study, we retrospectively compared the efficacy and safety of oral GCS combined with intravenous CTX and oral GCS alone in the treatment of MPGN-IgAN and NS and found that oral GCS combined with intravenous CTX had better efficacy than and similar safety to oral GCS alone, which needs further validation in a prospectively designed study.

MATERIALS AND METHODS

Research ethics statement

This study was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine and was designed in accordance with the principles of the Helsinki Declaration II. Written informed consent was obtained from all participants.

Patients

A retrospective study involving patients diagnosed with primary IgAN at Ruijin Hospital from January 2002 to December 2020 was conducted. The inclusion criteria were as follows: (i) males or females at least 14 years old; (ii) primary IgAN diagnosed by a renal biopsy with histological features of MPGN-IgAN; (iii) the presence of edema, total urinary protein (U-TP) >3.5 g/24 h and serum albumin <35 g/L; (iv) the follow-up period was at least 6 months; (v) eGFR ≥15 mL/min/1.73 m^2 at the time of biopsy; and (vi) treatment with GCS + CTX or GCS. The exclusion criteria were as follows: (i) IgAN secondary to a systemic disease, such as Henoch–Schönlein purpura, systemic lupus erythematosus or active hepatitis B; (ii) renal pathology coexisting with diabetic nephropathy, membranous nephropathy or other lesions; (iii) a proportion of crescent of ≥50%; (iv) newly diagnosed malignant tumor (within 3 years) or ongoing chemotherapy, radiation therapy or biological therapy; and/or (v) serum antineutrophil cytoplasmic antibody positivity. The recruited patients in the GCS + CTX or GCS groups were rather matched at a 1:1 ratio by propensity score matching (PSM) based on age, sex, U-TP, eGFR, mean arterial pressure (MAP) and MEST-C score (Fig. 1).

Data collection

Demographic data, including sex and age at biopsy, were collected. Clinical parameters that were collected included MAP, U-TP, serum albumin, serum creatine (Scr) and eGFR. Hypertension was diagnosed if systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate eGFR [19]. The histological findings were graded according to the histological grading criteria of the Oxford classification of IgAN [20].

Treatment

Patients from the GCS group were taking prednisone at a dose of 0.8–1 mg/kg per day (>30 mg/day), which was tapered off over the course of 6–8 months. Patients from the GCS + CTX group were treated with intravenous CTX (0.6–1.0 g monthly for 8–12 months, accumulated dose >6–8 g) combined with oral prednisone at a dose of 0.6–0.8 mg/kg per day (>25 mg/day).

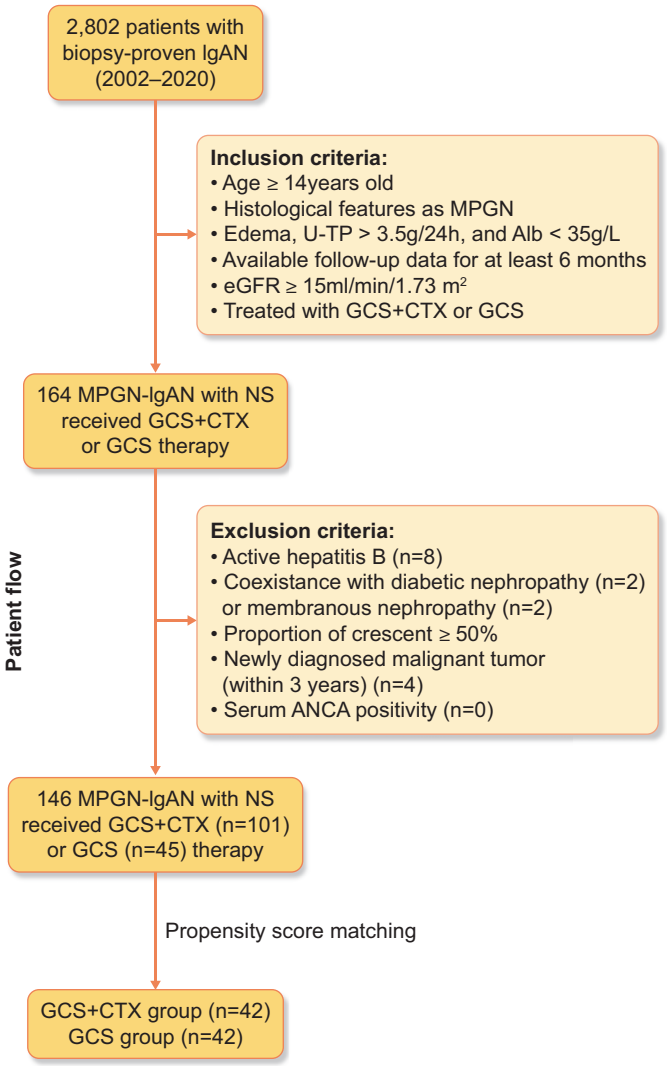


Figure 1: Study recruitment flowchart. Alb, serum albumin; ANCA, Anti-neutrophil cytoplasmic antibodies.

The patients were followed up monthly until they were given other immunosuppressive agents.

Definition

NS was defined as the presence of edema, U-TP >3.5 g/24 h and serum albumin <35 g/L [7, 9]. CR was defined as U-TP <0.3 g/24 h and a decline in eGFR <25% compared with baseline. PR was defined as a >50% reduction in U-TP compared with baseline, U-TP ≤3.5 g/24 h and a decline in eGFR <25%. No response (NR) was defined as a <50% reduction in U-TP or U-TP >3.5 g/24 h after treatment. The renal endpoint was defined as either a 50% decline in eGFR or a doubling of Scr, or ESKD. The degree of renal interstitial inflammation was classified as none/mild (0%–25%), moderate (26%–50%) or severe (>50%).

Statistical analyses

Normally distributed data are presented as the mean ± standard deviation, and nonparametric data are presented as the median and interquartile range. Student's *t*-test was used to compare the continuous parameters for normally distributed data, and the Mann–Whitney U test was used for skewed data. The chi-square test was used to compare categorical data. PSM was used to adjust for the differences in clinical and histological parameters between the two groups. Matching was performed using 1:1 matching (the nearest-neighbor matching method with a 0.2 caliper width) based on age, sex, U-TP, eGFR, MAP and MEST-C score. The cumulative renal survival rate until progression to a combined event was calculated and compared by the Kaplan–Meier method and log–rank test. Cox regression models were built to identify independent risk factors for renal endpoints. The proportional hazard assumption for the selected variables retained in the final model was originally checked by log minus log plots baseline hazard ratio (HR). A *P*-value <.05 was considered statistically significant. Statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA). GraphPad Prism Version 6 software (GraphPad Software, San Diego, CA, USA) was used for diagram preparation.

Table 1: Baseline characteristics of the recruited IgAN patients treated with GCS + CTX or GCS after PSM.

Variables	GCS + CTX group ($n = 42$)	GCS group ($n = 42$)
Onset age (years)	32.3 ± 14.1	31.7 ± 11.8
Diagnosed age (years)	36.1 ± 12.9	33.9 ± 12.0
Male, *n* (%)	18 (42.9)	20 (47.6)
BMI (kg/m^2)	23.5 ± 4.2	23.7 ± 3.6
MAP (mmHg)	98.1 ± 12.3	99.8 ± 13.4
Follow-up time (months)	32.3 (24.3, 53.1)	26.0 (9.9, 46.4)
Hb (g/L)	124.1 ± 19.8	127.3 ± 17.2
Scr (μmol/L)	99.0 (73.5, 155.0)	103.0 (82.3, 148.5)
eGFR (mL/min/1.73 m^2)	67.8 (42.7, 99.5)	66.7 (45.0, 96.2)
Alb (g/L)	28.0 (22.8, 29.0)	29.0 (26.0, 30.0)
U-TP (g/24 h)	4.9 (4.0, 6.3)	4.6 (3.9, 5.5)
Hypertension, *n* (%)	22 (52.4)	18 (42.9)
Diabetes, *n* (%)	3 (7.1)	2 (4.8)
ACEI/ARB, *n* (%)	36 (85.7)	35 (83.3)
Starting dose of GCS (mg)	40.0 (38.8, 50.0)	50.0 (40.0, 55.0)*
Cumulative dose of CTX (g)	6.4 (4.8, 8.0)	0
Oxford classification, *n* (%)		
M1	23 (54.8)	28 (66.7)
E1	21 (50.0)	21 (50.0)
S1	38 (90.5)	40 (95.2)
T1 + T2	20 (47.6)	14 (33.3)
C1 + C2	30 (71.4)	23 (54.8)
Glomerular sclerosis (≥25%), *n* (%)	16 (38.1)	14 (33.3)
Interstitial inflammation (≥25%), *n* (%)	24 (57.1)	16 (38.1)

Normally distributed data are presented as mean ± standard deviation , and nonparametric data are presented as median (interquartile range).
ACEI, angiotensin-converting enzyme inhibitor; Alb, serum albumin; ARB, angiotensin-receptor blocker; BMI, body mass index; C, crescents; E, endocapillary hypercellularity; Hb, hemoglobin; M, mesangial hypercellularity; S, segmental glomerulosclerosis or adhesion; T, tubular atrophy/interstitial fibrosis.
*$P < 0.05$.

RESULTS

Baseline characteristics

There were 84 patients recruited and assigned to either GCS + CTX ($N = 42$) or GCS ($N = 42$) groups at a 1:1 ratio by PSM based on age, sex, eGFR, MAP, U-TP and MEST-C score by Oxford classification (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. Patients from the GCS group and patients from the GCS + CTX group had similar baseline clinical and pathological characteristics, including onset age, male ratio, body mass index, MAP, hemoglobin, eGFR, U-TP, coexistence with diabetes, usage of angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker , and Oxford M1, E1, S1, T1/2 and C1/2. In addition, the starting dose of prednisone in the GCS + CTX group was lower than that in the GCS group (40 mg/day vs 50 mg/day, $P < .05$). The initiating dosage of GCS and cumulative dosage of CTX of the recruited IgAN patients treated with GCS + CTX or GCS are shown in Supplementary data, Table S1.

The baseline characteristics of 146 MPGN-IgAN patients before PSM are also shown in Supplementary data, Table S2. The excluded patients ($N = 62$) had lower hemoglobin (116.7 ± 18.6 vs 125.7 ± 18.5, $P = .004$), eGFR [35.0 (26.0, 47.3) vs 66.7 (43.0, 97), $P < .001$], higher percentage of T1/2 (79.0% vs 40.5%, $P < .01$), more moderate/severe glomerular sclerosis (58.1% vs 35.7%, $P = .007$) and more moderate/severe interstitial inflammation (79.0% vs 47.6%, $P < .001$) than patients included in the study (Supplementary data, Table S3). The jitter of propensity score distribution before and after matching is shown in Supplementary data, Fig. S1.

Table 2: Remission rates of the GCS + CTX and GCS group at Months 6, 12 and 24.

Remission rate	GCS + CTX group	GCS group	*P*-value
Month 6, *n* (%)	$n = 42$	$n = 42$	
CR	5 (11.0)	3 (7.1)	.71
PR	32 (76.2)	19 (45.2)	.004
CR + PR	37 (88.1)	22 (52.4)	<.001
Month 12, *n* (%)	$n = 42$	$n = 41$	
CR	10 (23.8)	7 (17.1)	.45
PR	27 (64.3)	16 (39.0)	.02
CR + PR	37 (88.1)	23 (56.1)	.001
Month 24, *n* (%)	$n = 40$	$n = 40$	
CR	13 (32.5)	4 (10.0)	.01
PR	21 (52.5)	15 (37.5)	.18
CR + PR	34 (85.0)	19 (47.5)	<.001

Treatment and proteinuria response

Among all 84 MPGN-IgAN patients, the remission rate (CR + PR) was higher in the GCS + CTX group than in the GCS group at Month 6 (88.1% vs 52.4%, $P < .001$), Month 12 (88.1% vs 56.1%, $P = .001$) and Month 24 (85.0% vs 47.5%, $P < .001$). In addition, the CR rate in the GCS + CTX group increased over time and was significantly higher than that in the GCS group at Month 24 (32.5% vs 10.0%, $P = .01$) (Table 2). Subgroup analysis showed that the higher response rate at Month 24 in the GCS + CTX group than in the GCS group was similar in different subgroups defined by sex, age, eGFR or Oxford MEST-C (Fig. 2).

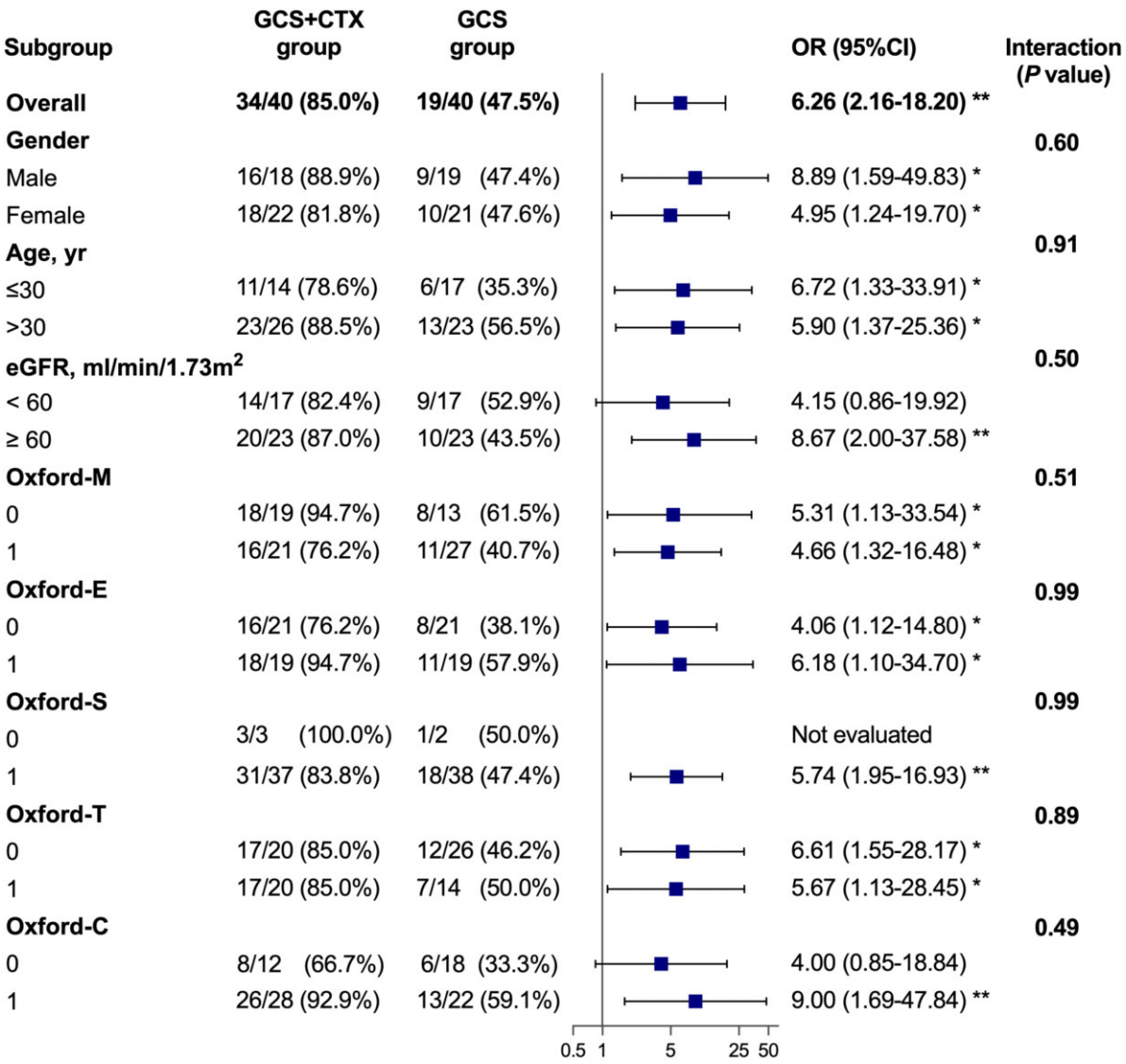


Figure 2: Logistic regression to compare the remission rates of the GCS + CTX vs GCS group at Month 24 according to subgroup analyses. Number of individuals, events, odd ratios (ORs), 95% CIs and *P*-values are shown for the GCS + CTX vs GCS treatment. Subgroup analysis was conducted by first restricting the population (e.g. considering only male patients). The same analysis (the main analysis for overall patients) was then applied to each subgroup. Notes: the patients in S0 group were too small to evaluated. C, crescents; E, endocapillary hypercellularity; M, mesangial hypercellularity; S, segmental glomerulosclerosis or adhesion; T, tubular atrophy/interstitial fibrosis. *$P < .05$; **$P < .01$.

Furthermore, we found that the reduction in U-TP in patients from the GCS + CTX group was greater at Month 6 [–3.4 (–4.9, –3.0) vs –2.8 (–3.8, –1.5) g/24 h, $P = .001$], Month 12 [–4.1 (–5.3, –3.2) vs –2.9 (–4.2, –1.8) g/24 h, $P = .001$] and Month 24 [–3.9 (–5.0, –3.0) vs –2.6 (–3.8, –1.6) g/24 h, $P = .001$] than that in patients from the GCS group (Fig. 3a). The trend of greater reduction in U-TP in the GCS + CTX group than in the GCS group was similar in different subgroups defined by sex (Fig. 3b and c) and age (Fig. 3d and e).

In addition, 58 patients met the criteria of having U-TP >3.5 g/24 h and Alb <30 g/L. Among them, 33 patients were treated with GCS + CTX, and 25 patients were only treated with GCS. Baseline clinical and pathological characteristics were similar between the two groups (Supplementary data, Table S4). Similarly, the remission rate (CR + PR) was higher in the GCS + CTX group than in the GCS group at Month 6 (84.8% vs 52.0%, $P = .01$), Month 12 (87.9% vs 54.2%, $P = .004$) and Month 24 (87.1% vs 47.8%, $P = .002$) (Supplementary data, Table S5).

Kidney function progression

During the follow-up period, 2/42 (4.8%) in the GCS + CTX group and 8/42 (19.0%) in the GCS group reached the composite endpoint. According to the Kaplan–Meier analysis, the overall 5-year endpoint-free rate of patients from the GCS + CTX group was higher than that of patients from the GCS group (90.9% vs 51.7%, $P = .02$) (Fig. 4a). We further compared the rate of annual eGFR decline in the two groups and the results indicated that eGFR decreased at a lower rate in patients from the GCS + CTX group than in patients from the GCS group [eGFR slope: 0.05 (–3.09, 3.67) vs –2.56 (–11.30, 0.86) mL/min/1.73 m^2/year, $P = .03$] (Fig. 4b). The univariable Cox regression analysis showed that

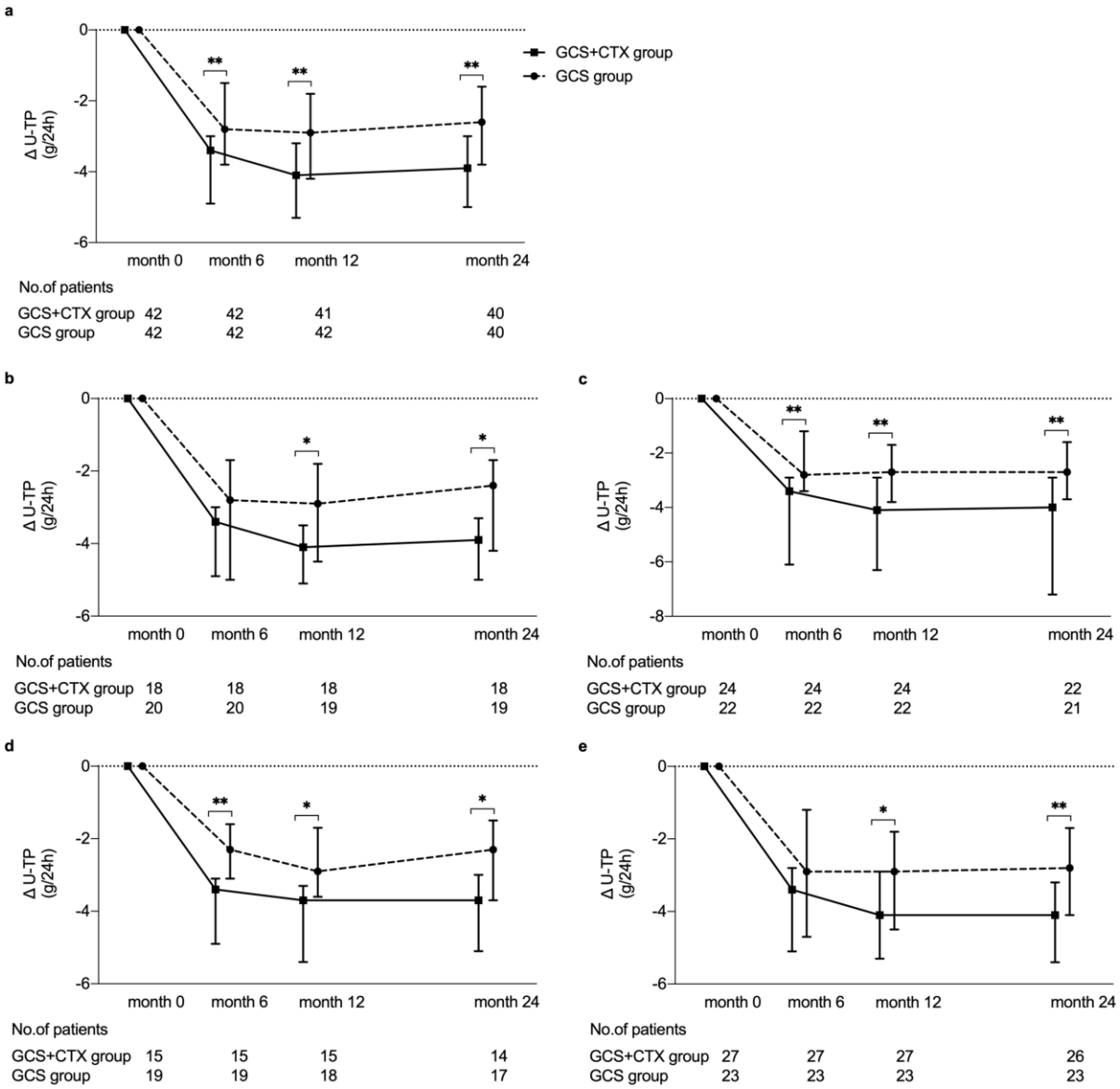


Figure 3: Change of U-TP in whole cohort and different subgroups during the follow-up period. (**a**) Change of U-TP in whole cohort; (**b**) change of U-TP in male patients; (**c**) change of U-TP in female patients; (**d**) change of U-TP in patients of age ≤30 years; (**e**) change of U-TP in patients of age >30 years. The dots represent the median value of change in U-TP (Δ U-TP); The bars represent the 25th and 75th percentiles. *$P < .05$; **$P < .01$.

GCS + CTX treatment was associated with a lower risk for renal function progression at 5 years than GCS treatment [Model 1, HR = 0.20, 95% confidence interval (CI) 0.04–0.93]. Based on multivariate Cox regression analysis, unlike GCS treatment alone, GCS + CTX treatment was independently associated with a decrease in risk for the composite endpoint after adjusting for age and sex (Model 2, HR = 0.18, 95% CI 0.04–0.90) and when using the full model International Risk Prediction Score without race (Model 3, HR = 0.20, 95% CI 0.04–0.94) and with race (Model 4, HR = 0.17, 95% CI 0.04–0.83) (Table 3) [21].

The proportional hazard assumption for therapy variable was checked by log(-log) plot (Supplementary data, Fig. S2). Two survival curves roughly parallel to examine the role of the risk factor for survival of the proportion of change in different time points, and two groups (CS and CS + CTX group) had equally proportional changes in survival risk, which did not change over time.

Safety and adverse events

Total adverse event (AE) rates were similar between the GCS + CTX and GCS groups [50.0% (21 of 42) vs 42.9% (18 of 42), $P = .51$], and there was no difference in severe AEs between the two groups [7.1% (3 of 42) vs 11.9% (5 of 42), $P = .71$; Table 4]. The types of infections reported in the two groups included upper respiratory tract infection (21.4% vs 19.0%, $P = .79$), infection with varicella zoster virus (2.4% vs 0.0%, $P = 1.00$), fungal infection of tinea pedis (7.1% vs 0.0%, $P = .24$) and urinary tract infection (14.3% vs 4.8%, $P = .28$). No deaths occurred in either treatment group.

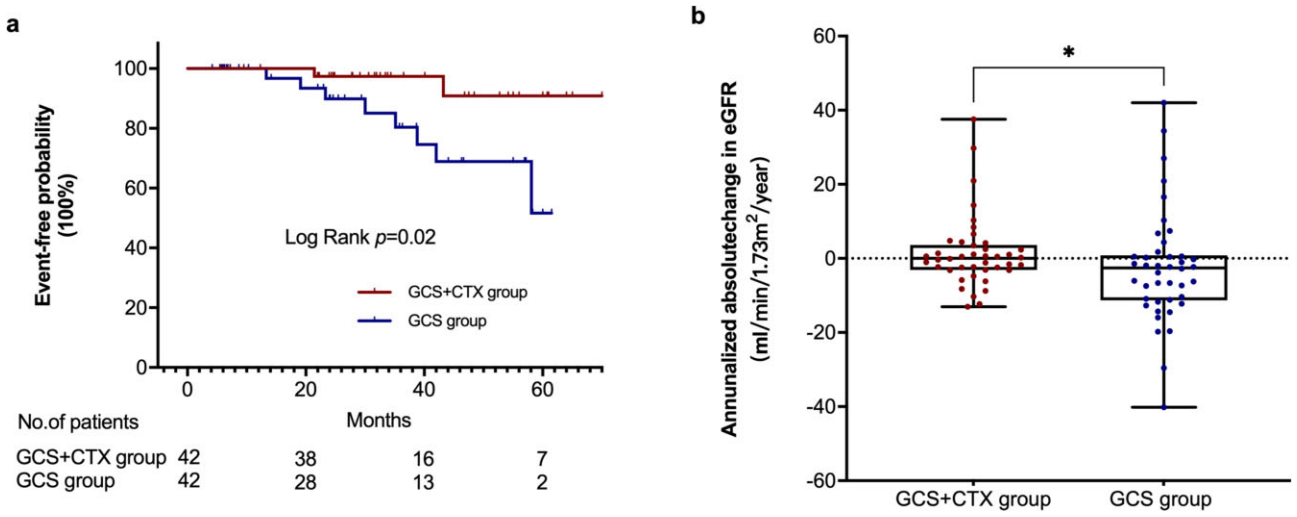


Figure 4: Kaplan–Meier survival analysis of the combined event and eGFR annual change rates during the follow-up period in the GCS + CTX and GCS group. (**a**) Kaplan–Meier survival analysis of the combined event (≥50% decline of eGFR, doubling of Scr or progression to ESKD) for patients in GCS + CTX and GCS groups during the 5 years' follow-up; (**b**) box plots overlaid with scatterplots of eGFR annual change rates during the follow-up period in the GCS + CTX and GCS group. *$P < .05$.

Table 3: Cox proportional hazards analysis for the association between the therapy (GCS + CTX versus GCS) and renal survival in IgAN patients during 5 years.

	No. of individuals	No. of renal events	HR (95% CI)	*P*-value
Model 1	84	10	0.20 (0.04–0.93)	.041*
Model 2	84	10	0.18 (0.04–0.90)	.036*
Model 3	84	10	0.20 (0.04–0.94)	.041*
Model 4	84	10	0.17 (0.04–0.83)	.028*

Model 1 was unadjusted;
Model 2 was adjusted for age and sex;
Model 3 was adjusted for risk scores calculated by the full model without race of international risk prediction in IgAN;
Model 4 was adjusted for risk scores calculated by the full model with race of international risk prediction in IgAN.
The patients were followed up after the diagnosis was made by renal biopsy. The event was a 50% decline of eGFR, doubling of Scr or progression to ESKD.
*$P < 0.05$.

DISCUSSION

NS is a rare clinical condition in patients with IgAN. Previous studies have revealed that IgAN patients with NS are at an increased risk for disease progression if clinical remission cannot be achieved [22, 23]. Patients with IgAN-related NS usually have two common pathologic types, MCD and MPGN, which have different response rates to GCS therapy and risks for ESKD. MCD-IgAN has been shown to respond well to GCS and should be treated as MCD according to the 2021 KDIGO guidelines [13]. Unlike MCD-IgAN, the treatment strategy for patients with MPGN-IgAN with NS is not clear, and nephrologists are often required to treat them empirically. To the best of our knowledge, this is the first study to compare the efficacy and safety of GCS combined with CTX versus GCS alone for the treatment of MPGN-IgAN patients with NS. In this study, we found that the combination of GCS and CTX was more effective in reducing urinary protein and was associated with a decreased risk for renal function progression than GCS alone in the treatment of MPGN-IgAN patients with NS. Furthermore, we found that patients who received a combination of GCS and CTX had less GCS exposure, and the treatment had good tolerability.

A considerable portion of IgAN patients develop the disease after upper respiratory or gastrointestinal infections, suggesting that mucosal infections play an important role in IgAN pathogenesis [24, 25]. It has been proposed that excessive intestinal production of Gd-IgA1 due to abnormal intestinal mucosal immunity plays a key role in disease pathogenesis [26]. This hypothesis has now been further confirmed by the targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN) study on Nefecon, a novel targeted release formulation of budesonide designed to deliver the drug to the distal ileum in IgAN patients. The NEFIGAN study, which is a phase II clinical study of Nefecon, showed that Nefecon can further reduce proteinuria on the basis of renin–angiotensin–aldosterone system inhibitor (RASi) therapy. Notably, the adverse effects associated with Nefecon were similar to those in the placebo control group and showed a favorable safety profile [5]. Most recently, the results of Part A of the phase 3 efficacy and safety of Nefecon in patients with primary IgA nephropathy (NefIgArd) trial were released. The NefIgArd trial tested the efficacy and safety of 9 months of treatment with Nefecon (16 mg/day) versus placebo in IgAN patients. At 9 months after treatment initiation (Part A), the 24-h urine protein-to-creatinine ratio was 27% lower and eGFR decline was 3.87 mL/min/1.73 m^2 slower in the Nefecon group than in the placebo group, and the treatment was well tolerated [27].

Unlike intestinal local steroid therapy, the use of systemic steroid therapy in IgAN patients has been highly controversial. Two important studies focusing on the efficacy and safety of steroid therapy were conducted in Europeans (STOP-IgAN study) and in a predominantly Asian population (TESTING study). Although the two studies failed to reach an agreement on whether steroids can further inhibit renal function progression on the basis of RASi therapy and strict blood pressure control, both studies found that steroids could increase the risk of infection, especially serious infections in IgAN patients, which caused the early termination of the TESTING study [16, 17]. Thereafter, the TESTING study changed the regimen to reduce the dose of oral steroids from moderate doses (0.6–0.8 mg/kg/day) to low doses

Table 4: Summary of adverse events.

	GCS + CTX group ($n = 42$)	GCS group ($n = 42$)	P-value
Total SAEs, *n* (%)	3 (7.1)	5 (11.9)	.71
Pneumonia	1 (2.4)	3 (7.1)	.61
Osteonecrosis of the femoral head	1 (2.4)	0 (0)	1.00
Newly diagnosed diabetes	1 (2.4)	2 (4.8)	1.00
Total AEs (including SAEs), *n* (%)	21 (50.0)	18 (42.9)	.51
Infections	18 (42.9)	12 (28.6)	.17
Pneumonia	1 (2.4)	3 (7.1)	.61
Upper respiratory tract infection	9 (21.4)	8 (19.0)	.79
Varicella zoster virus	1 (2.4)	0 (0)	1.00
Fungal infection of tinea pedis	3 (7.1)	0 (0)	.24
Urinary tract infection	6 (14.3)	2 (4.8)	.28
Osteoporosis	1 (2.4)	2 (4.8)	1.00
Increase of liver enzymes	4 (9.5)	0 (0)	.12
Menstrual abnormalities	2 (4.8)	0 (0)	.47
Thrombocytopenia	1 (2.4)	0 (0)	1.00
Insomnia	0 (0)	1 (2.4)	1.00
Gastrointestinal symptoms	0 (0)	3 (7.1)	.24

Multiple occurrences of the same AE in one person were only counted once. P-value for comparisons between the number of patients in the GCS + CTX group and the number of patients in the GCS group.
SAE, serious adverse event.

(0.4 mg/kg/day) and found that low doses of steroids had a similar effect on slowing renal function progression while significantly reducing infection-related AEs [28]. Notably, neither of the studies focused on the treatment of IgAN patients with NS and even excluded them from the study, resulting in a lack of evidence for immunosuppressive treatment in this subset of IgAN patients.

An observational study from China revealed that MPGN-IgAN patients with NS had more severe renal histopathological lesions than non-NS IgAN patients, including more endocapillary hypercellularity (E1 17% vs 3.6%), interstitial fibrosis (T1/2 38.6% vs 25.2%) and crescents (C1/2 37.4% vs 26.8%), but less segmental glomerulosclerosis or adhesion (S1 49.7% vs 59.7%) and global sclerosis (G 75.4% vs 81.9%), resulting in more renal endpoints in the MPGN-IgAN group than in the non-NS IgAN group (29.8% vs 15.8%) after an average follow-up of 44 months [6]. These results suggest that MPGN-IgAN patients with NS should be treated more aggressively since patients usually have more severe clinical-histological presentations and a higher risk of progression to renal failure. RASi therapy is recognized as the standard treatment for IgAN, which is obviously not sufficient for patients presenting with NS [29, 30]. Although clinicians prefer to use immunosuppressive therapy for these patients, treatment is often empirical, and it is unclear how to choose between the use of GCS alone and GCS in combination with immunosuppressants.

In this study, we focused on the efficacy and safety of immunosuppressive therapy in patients with MPGN-IgAN with NS. The strategy of the combination of GCS and CTX used in our study is consistent with the treatment strategy used in a study by Ballardie and Roberts [31]. We found that patients treated with GCS combined with intravenous CTX therapy had a higher remission rate than those treated with GCS monotherapy at Month 6 (88.1% vs 52.4%, $P = .001$), Month 12 (88.1% vs 56.1%, $P = .001$) and Month 24 (85.0% vs 47.5%, $P = .001$). In addition, we also performed a sensitivity analysis by excluding IgAN patients with Alb $\geq$30 g/L, and similar results were obtained. Moreover, subgroup analysis once again confirmed that GCS combined with CTX was more effective than GCS monotherapy in different populations. Furthermore, there was no difference between the GCS + CTX and GCS groups in terms of total AEs [50% vs 42.9%, $P = .51$]. Additionally, the two groups had similar infection-related AEs; although the infection rate was slightly higher in the GCS + CTX group, the difference was not statistically significant, and the majority of AEs were upper respiratory and urinary tract infections that were cured after anti-infection treatment. Although we found no difference in infection-related adverse events between the two groups, steroid and immunosuppressant therapy should be applied very carefully in IgAN patients. Both the TESTING and STOP-IgAN studies have determined that steroids can lead to more infection-related adverse events than conservative therapy. In addition, most of our patients were young. Among 84 patients, only 3 were older than 60 years. Thus, our findings need to be validated in older IgAN patients before they can be applied in those patients. Nevertheless, the adverse effect of immunosuppressants for IgAN patients cannot be ignored, and the immune system and potential infection should be carefully evaluated before initiating those treatments.

Previous studies reported that CTX was more effective in IgAN patients with active renal lesions, particularly in patients with crescents. In a small sample size study based on 20 IgAN patients with diffuse mesangial proliferation and crescent formation, 12 patients were given oral GCS combined with oral CTX (1.5 mg/kg/day) for 8 weeks, and another 8 patients did not receive immunosuppressive therapy. The authors reported a higher 5-year renal survival rate in the GCS + CTX group than in the control group (91.6% vs 37.5%, $P = .01$) [32]. This study suggests that for IgAN patients with active renal lesions, GCS + CTX may be more effective in delaying disease progression than non-immunosuppressive therapy. In our study, we compared the benefit of GCS + CTX with that of GCS alone in different subgroups of patients with or without crescents, and found that the benefit of GCS + CTX treatment was higher in IgAN patients with crescents than in patients without crescents, but the interaction analysis did not suggest that the difference was statistically significant.

The main limitations of our study are as follows. First, it used a retrospective study design. To reduce the influence of potential confounding factors on the results, we used PSM to balance

the major confounders, including age, sex, blood pressure, urine protein, renal function and Oxford MEST-C. However, the impact of other potential confounders on the results cannot be ruled out. Second, due to the retrospective nature of this study, not all patients were treated with the same treatment protocols regarding dose, duration and tapering. Prospective design studies are needed to validate our findings in the future. Third, not all the patients in this study received optimized supportive care with RASi for at least 3 months prior to immunosuppression therapy initiation since some of them had severe edema at renal biopsy, and it was necessary to start immunosuppressant therapy as soon as possible to relieve nephrotic syndrome in a timely manner. Finally, the number of cases in this study was relatively small, especially after PSM pairing, which further reduced the limited number of cases. Considering that NS, especially MPGN-related NS, is very rare in patients with IgAN, our cohort remains the largest case–control study in this field to date, providing important evidence for the treatment of IgAN patients with clinical manifestations of NS and pathological manifestations of MPGN.

In conclusion, we found that oral GCS combined with intravenous CTX was more effective than oral GCS alone and had similar safety in the treatment of MPGN-IgAN patients with NS. However, prospective studies are needed to confirm these findings.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Study conception and design: J.X., Y.O., W.D. and Z.C.; data acquisition: W.D., Z.C., Z.F., J.L., Q.Z., L.X., H.Y. and Q.W.; data analysis and interpretation: W.D., Z.C., Z.F., X.G., H.S., H.R. and W.W.; statistical analysis: W.D., Z.C., X.G. and Z.W.; overall supervision and mentorship: J.X. and Y.O. Each author contributed important intellectual content during manuscript drafting or revision accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

All data included in this study are available upon request by contact with the corresponding author.

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