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Original Article

ORIGINAL ARTICLE

The predictive value and response to immunosuppressive therapy of IgA nephropathy patients with crescents in a large retrospective Chinese cohort

Yingman Guo [1], Sufang Shi[1], Xujie Zhou[1], Lijun Liu[1], Jicheng Lv[1], Li Zhu[1], Suxia Wang[1,2] and Hong Zhang[1]

[1]Renal Division, Department of Medicine, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Peking, China and [2]Electron Microscopy Laboratory, Peking University First Hospital, Peking, China

Correspondence to: Sufang Shi; E-mail: shisufang0510@163.com

ABSTRACT

Background. The prognostic value and response to immunosuppressive therapy (IST) of patients with crescents in the different backgrounds of pathological presentations in immunoglobulin A nephropathy (IgAN) is unclear.
Methods. A total of 1262 IgAN patients were enrolled. Crescents (C, 0/1/2), fibrinoid necrosis (FN, 0/1) and endocapillary hypercellularity (E, 0/1) were integrated into different degrees of glomerular activity (0–4 points): mild (0), moderate (1–2) and severe (≥3). The effect of IST on patients with different glomerular activity scores and chronic tubular and interstitial lesions (T, 0/1/2) were analysed using Cox regression analysis. The kidney outcome was defined as an estimated glomerular filtration rate decrease ≥30% or end-stage kidney disease.
Results. C2 was an independent risk factor for kidney outcomes {overall cohort: hazard ratio [HR] 1.85 [95% confidence interval (CI) 1.03–3.31], $P = .040$; T0 patients: HR 6.52 [95% CI 2.92–14.54], $P < .001$; reference to C0} in those without IST, while the HR decreased to 0.83 (95% CI 0.54–1.27; $P = .396$) in the overall cohort and 2.39 (95% CI 1.00–5.67; $P = .049$) in T0 patients with IST. For patients with severe glomerular activity, IST decreased the risk of kidney outcomes by 70% in the overall cohort [HR 0.30 (95% CI 0.12–0.74), $P = .009$; reference to those without IST] and 86% in T0 patients [HR 0.14 (95% CI 0.04–0.54), $P = 0.005$; reference to those without IST].
Conclusions. IST could reduce the risk for kidney outcomes in IgAN patients with C2 and T0 lesions together, as well as in those with crescents and at least one other active lesion, including FN and E1 lesions.

LAY SUMMARY

The evidence to make immunosuppressive therapy decisions according to the presence and number of crescents at the time of kidney biopsy is insufficient in immunoglobulin A nephropathy (IgAN). In the present study, crescents (C, 0/1/2), fibrinoid necrosis (FN, 0/1) and endocapillary hypercellularity (E, 0/1) were integrated into different degrees of

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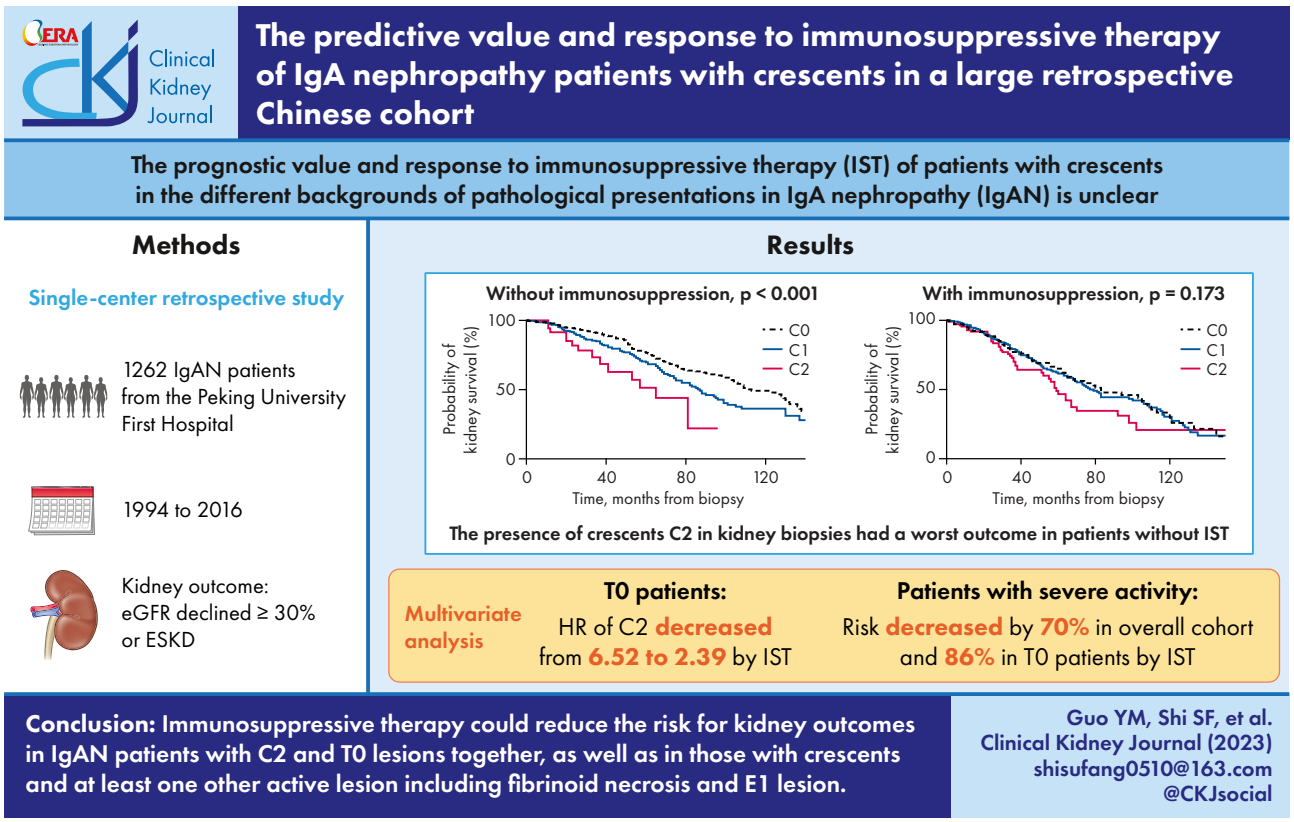
glomerular activity (0–4 points): mild (0), moderate (1–2) and severe (≥3). The effect of immunosuppressive therapy on patients with different degrees of glomerular activity and chronic tubular and interstitial lesions (T, 0/1/2) was analysed. Finally, our study suggested that immunosuppressive therapy could reduce the risk for poor kidney outcomes in IgAN patients with crescents, especially when these patients presented with at least one other active lesion, including fibrinoid necrosis and endocapillary hypercellularity lesions, or mild chronic tubular and interstitial lesions.

GRAPHICAL ABSTRACT



Keywords: crescent, IgA nephropathy, immunosuppressive therapy

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, with a wide range of histological patterns and complex clinical manifestations, and 20–30% of patients will develop to end-stage kidney disease (ESKD) within 10–20 years [1–3]. IgAN can only be diagnosed by histopathology, and the Oxford classification, i.e. the MEST-C scoring system, is the pathological classification system for IgAN that is used worldwide. The recently published 2021 Kidney Disease: Improving Global Outcomes clinical practice guidelines for the management of glomerular disease suggested that clinical and histological data at the time of biopsy can be used to risk stratify patients; however, there is insufficient evidence to support the use of the Oxford classification, including the presence and number of crescents, in determining whether immunosuppression should be used for treating IgAN patients [4].

A crescent is a kind of histological lesion that indicates rapid progression and suggests the need for immunosuppressive therapy in lupus nephritis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vacuole nephritis [5, 6]. In IgAN patients, Hass *et al.* [7] found that patients whose biopsy specimens showed crescents in ≥25% of glomeruli had a worse kidney outcome irrespective of immunosuppressive treatment. This evidence led to the incorporation of C scores in the revised Oxford classification: C0 (no crescents), C1(crescents in 1–24% of glomeruli) and C2 (crescents in ≥25% of glomeruli) [8]. However, subsequent studies have not been able to broadly confirm the results. Sehoon *et al.* [9] demonstrated that immunosuppressive therapy could not improve kidney survival in patients with C1 or C2 and Wei *et al.* [10]. found that patients with C2 lesions could also benefit from immunosuppression.

Crescents often coexist with other active lesions, including endocapillary hypercellularity and fibrinoid necrosis lesions,

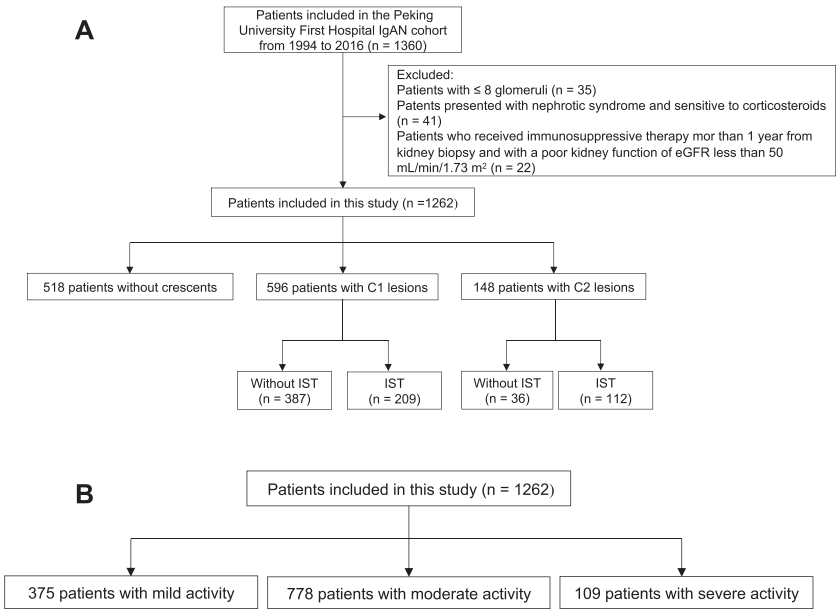


Figure 1 (A) and (B): Flow diagram of the study population.

and can be found in patients with different degrees of tubular atrophy or interstitial fibrosis lesions. Our previous study found that immunosuppressive therapy could significantly reduce the risk of poor kidney outcomes for IgAN patients with both fibrinoid necrosis and crescents or endocapillary hypercellularity lesions but not for those with fibrinoid necrosis lesions alone [11]. Moreover, Itami *et al*. [12] recently proposed a novel pathological scoring system that integrated active (M, E, S, C lesions) and chronic (T lesions) lesions in the Oxford classification, and they found that only those with highly active and mild chronic pathological lesions experienced a remarkable reduction in the risk of ESKD using immunosuppression. Therefore, whether the controversial predictive values of crescents are correlated with other active lesions or varied in different degrees of chronic background histological presentations requires further investigation. Therefore, in the present study we evaluated the predictive value and response to immunosuppressive therapy in IgAN patients with crescents with different degrees of background pathological presentations in a large Chinese cohort.

MATERIALS AND METHODS

Study design and population

In the present study, a total of 1360 patients were recruited from the Peking University First Hospital IgA Nephropathy Database. All patients received kidney biopsies from July 1994 to June 2016 and were followed up for at least 12 months. Patients with IgAN secondary to liver disease, lupus or Henoch–Schönlein purpura and IgAN superimposed on ANCA-associated necrotizing glomerulonephritis were excluded. There were no restrictions on initial estimated glomerular filtration rate (eGFR) or proteinuria. Patients who depended on dialysis were excluded. Thirty-five patients with fewer than eight glomeruli were excluded. Forty-one patients who presented with nephrotic syndrome and sensitive to corticosteroids were excluded due to the possibility of minimal change disease and IgA deposition. Twenty-two patients who received immunosuppressive therapy >1 year after kidney biopsy and whose eGFR had decreased significantly (to <50 ml/min/1.73 m^2) were excluded. In total, 1262 patients were enrolled in the present study (Fig. 1a). We further divided patients with crescents (C, 0/1/2), fibrinoid necrosis (FN, 0/1) and endocapillary hypercellularity (E, 0/1) into groups of different degrees of glomerular activity (0–4 points): mild (0), moderate (1–2) and severe (≥3). Ultimately, 375 patients showed mild activity, 778 patients showed moderate activity and 109 patients showed severe activity (Fig. 1b).

Baseline and follow-up clinical assessments, including demographic characteristics, eGFR, mean arterial pressure (MAP), haematuria and proteinuria, were recorded. All baseline clinical characteristics were obtained at the time of kidney biopsy. Written informed consent was obtained from all participants, and the protocol was reviewed and approved by the Ethics Committee of the Peking University First Hospital.

Definitions

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13]. MAP was calculated as diastolic blood pressure (BP) + 1/3(systolic BP − diastolic BP). Hypertension was defined as a systolic BP ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the use of antihypertension medication. Microscopic haematuria was evaluated in fresh urine using a fully automated urine particle analyser and expressed as total erythrocytes per microlitre. Time-averaged haematuria was defined as the mean of the average haematuria calculated every 6 months. The same methods were used for time-averaged proteinuria and time-averaged MAP.

Immunosuppressive therapy (IST) was defined as treatment with corticosteroids or steroids plus immunosuppressive agents, including cyclophosphamide (CYC), cyclosporine, azathioprine or mycophenolate mofetil (MMF), regardless of the duration or dose. No patient received rituximab or plasma exchange therapy. Renin–angiotensin system (RAS) blocker

therapy was defined as the use of an angiotensin-converting enzyme inhibitor and/or an angiotensin receptor blocker. The composite kidney endpoint in the retrospective cohort was defined as a ≥30% reduction in the eGFR, ESKD (eGFR <15 ml/min/1.73 m^2), kidney replacement therapy for at least 6 months or kidney transplantation.

Pathology review

All kidney biopsy specimens were processed routinely for immunofluorescence microscopy, light microscopy and electron microscopy. Sections were stained for direct immunofluorescence with fluorescein isothiocyanate–conjugated antibodies specific for human IgG, IgM, IgA, C1q, C3 and fibrinogen. Sections used for light microscopy were stained with haematoxylin and eosin (H&E), Masson's trichrome, periodic acid–Schiff (PAS) and PAS together with silver methenamine. The kidney biopsies were reviewed independently by two pathologists using the Oxford classification criteria who were blinded to the clinical data. Crescents were scored according to the Oxford pathological classification and the scoring method was as follows: the proportions of glomeruli with cellular or fibrocellular crescents in the total glomeruli: C0 (no crescents), C1 (<25%) and C2 (≥25%); the fibrous crescents were excluded [8, 14]. Fibrinoid necrosis was defined as a segmental deposition within and around the capillaries. Fibrinoid necrosis was scored as absent (0) or present (1).

Statistical analysis

Normally distributed variables are expressed as the mean ± standard deviation (SD) and were compared using Student's *t*-test. Non-parametric variables are expressed as the median and interquartile range (IQR) and were compared using a Mann–Whitney U test. To validate the predictive value of crescents, we used Kaplan–Meier survival curves and Cox regression to test the relationship between crescents and survival from a combined event. The multivariate Cox models addressed the predictive value of crescents adjusted for covariates (age, initial eGFR, MAP and proteinuria, and M, E, S and T lesions) and the proportional hazards assumptions of the Cox regression model were tested based on Schoenfeld residuals (phtest). The time to event was defined as the time from kidney biopsy to composite kidney endpoint if the patients progressed to the composite kidney endpoint or the time from kidney biopsy until the follow-up ended if the patients did not reach the composite kidney endpoint. The censored events mainly include that patients did not reach the composite kidney endpoint at the end of the follow-up or died of other reasons during the follow-up.

All *P*-values were two-tailed and values <.05 were considered statistically significant. Confidence intervals (CIs) included 95% of the predicted values. SPSS version 19 (IBM, Armonk, NY, USA) was used for all analyses.

RESULTS

Clinical and pathological characteristics of patients with different degrees of crescents

A total of 1262 IgAN patients were enrolled in the present study. Of these, 632 patients (50.1%) were female. The clinical and pathological characteristics of these patients are summarized in Table 1. At the time of kidney biopsy, the mean eGFR was 85 ± 31 ml/min/1.73 m^2 and the mean urine protein excretion was 1.24 g/24 h (95% CI 0.66–2.39). Patients were followed up for a median of 3.8 years (95% CI 2.0–6.8). In total, 596/1262 (47.2%) patients had C1, 148/1262 (11.7%) patients had C2 and only 28/1262 (2.22%) patients presented with crescents >50%. A total of 36.5% of patients (460/1262) received steroid and/or an immunosuppressive agent, including CYC, MMF or calcineurin inhibitors (CNIs). Among these patients, 43% (198/460) received steroid alone, the others received steroid and at least one kind of immunosuppressive agent. In the total cohort, 14.3% of patients (180/1262) received CYC, 5.4% (68/1262) received oral CNIs and 5.4% (68/126) received MMF. Also, 219/1262 (17.35%) patients received hydroxychloroquine.

Patients with C1/2 lesions showed a significantly lower eGFR (C2: 62 ± 31 ml/min/1.73 m^2; C1: 83 ± 29 ml/min/1.73 m^2; C0: 87 ± 29 ml/min/1.73 m^2), higher levels of haematuria [C2: 156.6 red blood cells (RBCs)/μl; C1: 119.4 RBCs/μl; C0: 62.1 RBCs/μl] and a higher prevalence of M1 lesions (C2: 56.1%; C1: 44.1%; C0: 31.9%), E1 lesions (C2: 50.0%; C1: 35.7%; C0: 24.7%), S1 lesions (C2: 68.9%; C1: 67.1%; C0: 58.9%) and T1/2 lesions (C2: 70.2%; C1: 36.7%; C0: 25.7%). Furthermore, patients with C1/2 lesions showed significantly more C3 deposition (C2: 83.8%; C1: 82.4%; C0 77.8%). Patients with C2 lesions had the most severe proteinuria (2.85 g/24 h) compared with the other two groups (C1: 1.20 g/24 h; C0: 1.05 g/24 h) and the highest proportion receiving immunosuppressive agents (C2: 75.7%; C1 35.1%; C0 26.8%). There was no significant difference in gender, age, the prevalence of hypertension or macroscopic haematuria among these three groups. A total of 119/1262 patients (9.4%) progressed to ESKD and 449/1262 patients (35.6%) progressed to the kidney composite endpoint (defined as a ≥30% decrease in the eGFR or ESKD). Patients with C2 lesions had the highest proportion of ESKD (C2: 15.5%; C1 8.6%; C0 8.7%; $P = .027$). IgAN patients with C1 and C2 lesions showed a significantly poorer prognosis than patients with C0 by Kaplan–Meier curve analysis ($P < .001$; Fig. 2a). However, multivariate Cox regression indicated that patients with C1 lesions [HR 1.13 (95% CI 0.92–1.38), $P = .255$, reference to C0] and C2 lesions [HR 1.26 (95% CI 0.92–1.73), $P = .158$, reference to C0] did not have a significantly higher risk of the kidney composite outcome than patients with C0 lesions after adjusting for age, eGFR, MAP, proteinuria at the time of biopsy, IST and MEST scores.

The prognostic value of different C scores in IgAN patients with or without immunosuppressive therapy

We further analysed the kidney prognosis of patients with different C scores with and without IST. The pathological presentations between C2 patients with and without IST were very similar, such as M1, E1 and S1 lesions, except T1/2 lesions were much more severe in C2 patients who received IST than those without IST. However, C1 patients who received IST showed significantly more severe M1, E1 and T1/2 lesions than those without IST. The prognosis was very similar between C2 patients with and without IST, while the prognosis of C1 patients who received IST was much poorer than for those without IST (Table 2).

There was no interaction between crescents and immunosuppressive therapy in the Cox regression model in the overall cohort ($P = .195$), T0 cohort ($P = .488$) and T1/2 cohort ($P = .350$). However, because the presence of crescents was always associated with IST therapy in IgAN, in the present study the patients were divided into groups according to with or without IST to investigate the relationship between crescents and response to IST, as a previous relevant study has done [7]. By multivariate

Table 1: Clinical and pathological characteristics of patients with different degrees of crescents.

Baseline characteristics	C0 ($n = 518$)	C1 ($n = 596$)	C2 ($n = 148$)
Female, % (n)	47.7 (247)	52.5 (313)	48.6 (72)
Age (years), mean ± SD	35 ± 12	35 ± 11	35 ± 14
MAP (mmHg), mean ± SD	94 ± 12	93 ± 12	96 ± 13[c]
eGFR (ml/min/1.73 m^2), mean ± SD	87 ± 29	83 ± 29	62 ± 31[b]
Proteinuria (g/24 h), median (IQR)	1.05 (0.57–1.99)[c]	1.20 (0.68–2.28)	2.85 (1.549–4.62)[a]
Proteinuria >1 g/24 h, % (n)	52.5 (272)	59.7 (356)	85.1 (126)[a]
Proteinuria >3.5 g/24 h, % (n)	10.7 (56)	11.7 (70)	39.9 (59)[a]
History of macroscopic haematuria, % (n)	26.8 (139)	29.2 (174)	27.0 (40)
Microscopic haematuria (RBCs/μl), median (IQR)	62.1 (23.1–198.5)	119.4 (47.3–351.3)	156.6 (78.7–582.6)[a]
Hypertension, % (n)	49.2 (255)	46.0 (274)	53.4 (79)
Pathology, % (n)			
M1	31.9 (165)	44.1 (263)	56.1 (83)[a]
E1	24.7 (128)	35.7 (213)	50.0 (74)
S1	58.9 (305)[b]	67.1 (400)	68.9 (102)
T1, T2	17.0, 7.5 (88, 39)	28.0, 8.7 (167, 52)	43.2, 27.0 (64, 40)[a]
Immunofluorescence findings, % (n)			
IgA ≥2+	96.3 (499)	97.8 (683)	98.0 (145)
IgG positive	10.2 (53)	14.3 (85)	13.5 (20)
IgM positive	54.8 (284)[b]	62.2 (371)	66.9 (99)
C3 ≥2+	77.8 (403)[c]	82.4 (491)	83.8 (124)
≥3+	44.4 (230)	48.5 (289)	42.6 (63)
Follow-up			
Length of follow-up (years), median (IQR)	4.3 (2.3–7.7)	3.6 (1.9–6.5)[c]	2.9 (1.8–5.3)[a]
Time-averaged proteinuria (g/24 h), median (IQR)	0.77 (0.41–1.33)	0.86 (0.50–1.39)	1.23 (0.69–2.26)[a]
Time-averaged haematuria (RBCs/μl), median (IQR)	51.7 (20.0–126.1)[a]	89.6 (35.1–187.4)	89.6 (39.3–172.0)
Treatment, % (n)			
Steroids or steroids with other IS agents	26.8 (139)	35.1 (209)	75.7 (112)[a]
Steroids alone	13.9 (72)	15.8 (94)	21.6 (32)
RAS blocker	95.9 (497)	97.5 (581)	97.3 (144)
Outcome, % (n)			
eGFR decrease ≥30%	34.2 (177)	34.9 (208)	39.9 (59)
eGFR decrease ≥50%	12.2 (63)	13.4 (80)	21.6 (32)[c]
ESKD	8.7 (45)	8.6 (51)	15.5 (23)[c]
Time to ESKD (years), median (IQR)	6.17 (3.71–8.92)[a]	4.17 (2.50–6.83)[c]	2.42 (1.58–3.33)
Slope eGFR (ml/min/1.73 m^2/year), mean ± SD	−2.81 ± 3.14	−3.09 ± 3.34	−3.32 ± 4.29
Composite kidney endpoint, % (n)	34.6 (179)	34.9 (208)	41.9 (62)

[a]$P < .001$ proteinuria, comparison between C2 and C0 or C1 group; microscopic haematuria, comparison between each of two groups; UTP >1 g/24 h, comparison between C2 and C0 or C1 group; UTP >3.5 g/24 h, comparison between C2 and C0 or C1 group; M1, comparison between each of two groups; E1, comparison between each of two groups; T1/2, comparison between each of two groups; length of follow-up, C2 group compared with C0 group; time-averaged proteinuria, comparison between C2 and C0 or C1 group; time-averaged haematuria, comparison between C0 and C1 or C2 group; steroids or steroids with other immunosuppressive agents, comparison between each of two groups; time to ESKD, C0 group compared with C2 group.

[b]$P < .01$ eGFR, comparison between each of two groups; IgM positive, comparison between C0 and C1 or C2 group; S1, comparison between C0 and C1 or C2 group.

[c]$P < .05$ proteinuria, C0 group compared with C1 group; MAP, C2 group compared with C1 group; C3 ≥2+, comparison between C0 and C1 or C2 group; length of follow-up, comparison between C1 and C0 or C2 group; eGFR decrease ≥50%, C2 group compared with C0 group; ESKD, the C2 group compared with C0 group; time to ESKD, C1 group compared with C2 group.

Composite kidney endpoint, defined by either a ≥30% reduction in the eGFR, ESKD (eGFR <15 ml/min/1.73 m^2), kidney replacement therapy for at least 6 months or kidney transplantation.

Cox regression analysis, the presence of C2 lesions was a significant risk factor for kidney outcome in patients without IST [HR 1.85 (95% CI 1.03–3.31), $P = .040$, reference to C0] and was not a significant risk factor in patients with IST [HR 0.83 (95% CI 0.54–1.27), reference to C0]. C1 lesions showed a borderline significant risk effect on kidney outcomes in patients who did not receive IST [HR 1.27 (95% CI 0.98–1.65), $P = .075$, reference to C0] and was not a significant risk factor in patients who received IST [HR 0.84 (95% CI 0.59–1.19), reference to C0] after adjusting for age, eGFR, MAP, proteinuria at the time of biopsy and MEST scores (Fig. 3).

The effect of IST on patients with different C lesions was analysed. By multivariate Cox regression analysis, IST was a borderline significant protective factor for kidney outcomes in IgAN patients with C2 lesions [HR 0.51 (95% CI 0.25–1.05), $P = 0.069$, reference to patients without IST] after adjusting for age, eGFR, MAP, proteinuria at the time of biopsy and MEST scores. However, IST did not reduce the risk of kidney outcomes in patients with C0 and C1 lesions (Supplementary Table S1).

These results indicated that the presence of crescents was an independent risk factor for kidney outcomes in IgAN patients without IST; however, IST did not provide benefits to IgAN patients with crescentic lesions. Chronic tubular and interstitial lesions might be one of the biases. Also, further analysis is needed as to whether other active glomerular lesions, including E1 and FN lesions, which are always correlated with crescents, could influence the effect of IST in IgAN patients with crescents.

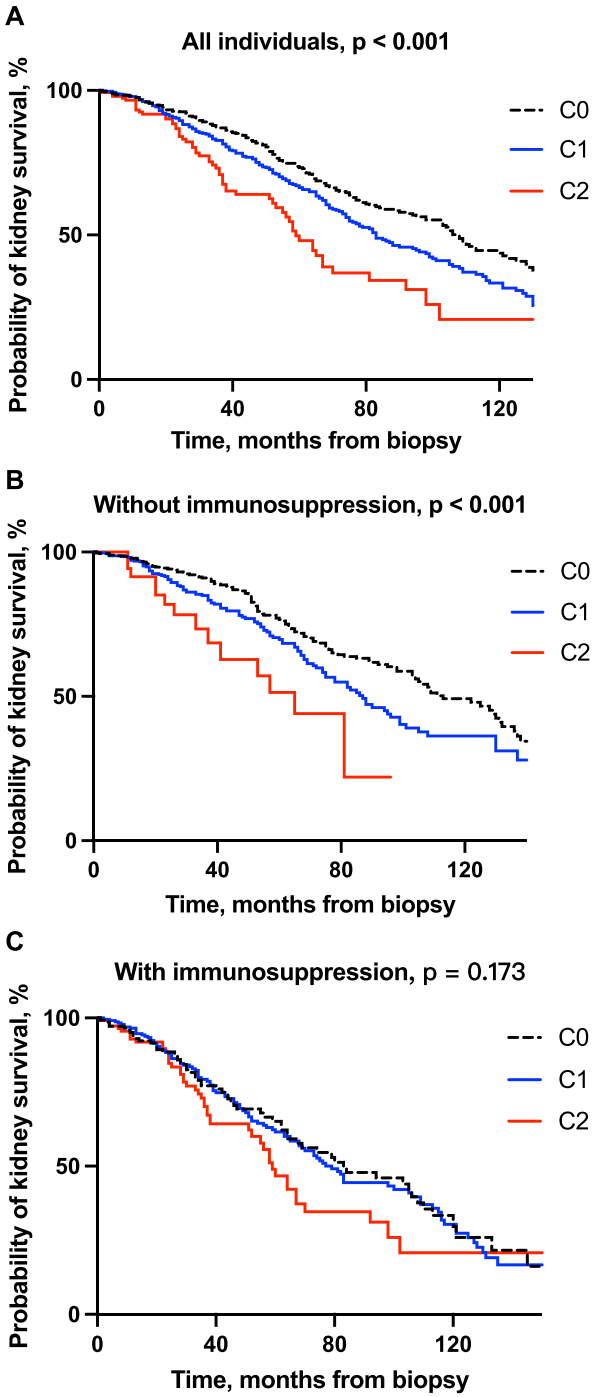


Figure 2: Kaplan–Meier curves for the composite kidney endpoint of patients with different C scores in **(A)** all individuals, **(B)** those who did not receive immunosuppression and **(C)** those who received immunosuppression.

The prognostic value of different C scores in IgAN patients with different T scores

T lesions have been confirmed to be the most powerful pathological lesion to indicate kidney outcomes in IgAN, and the presence of T lesions probably will influence the response to IST in patients with active lesions, so in the present study we investigate the response to IST of patients with C lesions in different degrees of chronic pathological lesions in our cohort.

Among the 812 patients with T0, 377/812 (46.4%) T0 patients showed C1 lesions and 44/812 (5.4%) showed C2 lesions. Patients with T0 and C1 lesions who received IST had more severe kidney disfunction, higher proteinuria and haematuria and more E1 lesions than those without IST. Patients with T0 and C2 lesions who received IST showed higher levels of proteinuria than those without IST. However, there was no significant difference in eGFR, haematuria or E1 lesions between patients with T0 and C2 lesions who received IST and those who did not receive IST. There was not a statistically significant difference in the kidney prognosis between C1 and C2 patients who did and did not receive IST in the T0 cohort (patients with C2: 34.5% versus 46.7%, $P = .431$; patients with C1: 31.4% versus 25.1%, $P = .221$).

By multivariate analysis, C2 was a significant high-risk factor for kidney outcomes in patients with T0 lesions [HR 3.61 (95% CI 2.03–6.43), $P < .001$, reference to C0], but the kidney outcomes of patients with C1 lesions were similar to those with C0 lesions [HR 1.20 (95% CI 0.91–1.59), $P = .192$, reference to C0] after adjusting for age, eGFR, MAP, proteinuria at the time of biopsy, IST and MES scores. In T0 patients without IST, C2 lesions had a 6.5-fold risk effect on kidney outcomes [HR 6.52 (95% CI 2.92–14.54), $P < .001$, reference to C0] and the risk decreased to 2.39 in T0 patients who received IST [HR 2.39 (95% CI 1.00–5.67), $P = .049$, reference to C0]. However, C1 was not a significant risk factor for kidney outcomes in T0 patients without IST [HR 1.29 (95% CI 0.97–1.78), $P = .130$, reference to C0] or with IST [HR 0.90 (95% CI 0.52–1.57), $P = .704$, reference to C0] after adjusting for age, eGFR, MAP, proteinuria at the time of biopsy and MES scores. Neither C1 nor C2 lesions had an effect on kidney outcomes in patients with T1/2 lesions, regardless of whether they received IST (Fig. 3).

The effect of IST on patients with different crescentic lesions and T0 was analysed. By multivariate Cox analysis, IST was a borderline significant protective factor for kidney outcomes in IgAN patients with C2 lesions and T0 [HR 0.24 (95% CI 0.05–1.11), $P = .067$, reference to patients without IST] (Supplementary Table S1).

Effect of immunosuppressive therapy on IgAN patients with different active glomerular lesions

We further investigated whether the effect of IST on IgAN patients with crescents correlated with other active glomerular lesions. Crescents, fibrinoid necrosis and endocapillary hypercellularity were integrated into different degrees of glomerular activity (0–4 points): mild (0), which indicated no active lesion; moderate (1–2), which indicated at least one active lesion; and severe (≥3), which indicated the presence of crescents and at least one other active lesion. Ultimately, 375 patients presented with mild activity, 778 presented with moderate activity and 109 presented with severe activity.

Compared with the other two groups, the severe activity group had the highest levels of proteinuria (severe: 2.78 g/24 h; moderate: 1.22 g/24 h; mild: 1.07 g/24 h) and microscopic haematuria (severe: 253.9 RBCs/μl; moderate: 112.1 RBCs/μl; mild: 59.6 RBCs/μl), and lower eGFR (severe: 70 ml/min/1.73 m^2; moderate: 82 ml/min/1.73 m^2; mild: 87 ml/min/1.73 m^2). Patients with severe activity showed a higher proportion of T1/2 lesions (severe: 56.8%; moderate: 36.8%; mild: 27.2%) and receiving IST (severe: 80.7%; moderate: 34.8%; mild: 26.9%). Patients with severe activity had a higher proportion of eGFR decreases ≥50 ml/min/1.73 m^2 (severe: 20.2%; moderate: 14.5%; mild: 10.7%). However, there were no significant differences in the

Table 2: Clinical and pathological differences between patients in the C1/2 cohort with or without immunosuppression.

Characteristics	Patients with C1 lesions (596)			Patients with C2 lesions (148)		
	Without immuno-suppression ($n = 387$)	With immuno-suppression ($n = 209$)	*P*-value	Without immuno-suppression ($n = 36$)	With immuno-suppression ($n = 112$)	*P*-value
Female, % (*n*)	55.6 (215)	46.9 (98)	0.043	50.0 (18)	48.2 (54)	0.852
Age (years), mean ± SD	35 ± 11	34 ± 12	0.086	40 ± 12	34 ± 14	0.011
MAP (mmHg) , mean ± SD	93 ± 12	94 ± 12	0.220	91 ± 12	97 ± 13	0.013
eGFR (ml/min/1.73 m^2), mean ± SD	89 ± 27	71 ± 30	<0.001	72 ± 30	59 ± 31	0.036
Proteinuria (g/24 h), median (IQR)	1.04 (0.58–1.76)	1.93 (1.00–3.61)	<0.001	1.45 (0.89–2.34)	3.39 (1.80–5.00)	<0.001
History of macroscopic haematuria, % (*n*)	27.4 (106)	32.5 (68)	0.187	25.0 (9)	27.7 (31)	0.753
Microscopic haematuria (RBCs/µl), median (IQR)	100.2 (41.6–262.0)	186.0 (60.4–489.3)	<0.001	78.9 (44.2–170.8)	221.8 (107.5–690.0)	<0.001
Hypertension, % (*n*)	44.4 (172)	48.8 (102)	0.308	52.8 (19)	53.6 (60)	0.934
Pathology, % (*n*)						
M1	40.6 (157)	50.7 (106)	0.017	61.1 (22)	54.5 (61)	0.485
E1	32.0 (124)	42.6 (89)	0.010	36.1 (13)	54.5 (61)	0.055
S1	66.1 (256)	68.9 (144)	0.495	80.6 (29)	65.2 (73)	0.083
T1, T2	25.1, 3.9 (97, 15)	33.5, 17.7 (70, 37)	<0.001	47.2, 11.1 (17, 4)	42.0, 32.1 (47, 36)	0.032
Time-averaged proteinuria (g/24 h), median (IQR)	0.77 (0.46–1.17)	1.12 (0.61–1.73)	<0.001	1.13 (0.67–1.78)	1.32 (0.69–2.56)	0.228
Time-averaged haematuria (RBCs/µl), median (IQR)	91.0 (36.5–180.8)	81.5 (31.7–199.8)	0.634	76.3 (33.6–168.4)	93.0 (43.0–176.5)	0.604
Slope eGFR (ml/min/1.73 m^2/year), mean ± SD	−3.09 ± 2.90	−3.07 ± 4.02	0.936	−3.49 ± 2.42	3.27 ± 4.75	0.793
eGFR decrease ≥50%, % (*n*)	8.0 (31)	23.4 (49)	<0.001	13.9 (5)	24.1 (27)	0.195
ESKD, % (*n*)	4.7 (18)	15.8 (33)	<0.001	5.6 (2)	18.8 (21)	0.057
Composite kidney endpoint, % (*n*)	30.7 (119)	42.6 (89)	0.004	41.7 (15)	42.0 (47)	0.975

Composite kidney endpoint, defined by either a ≥30% reduction in the eGFR, ESKD (eGFR <15 ml/min/1.73 m^2), kidney replacement therapy for at least 6 months or kidney transplantation.

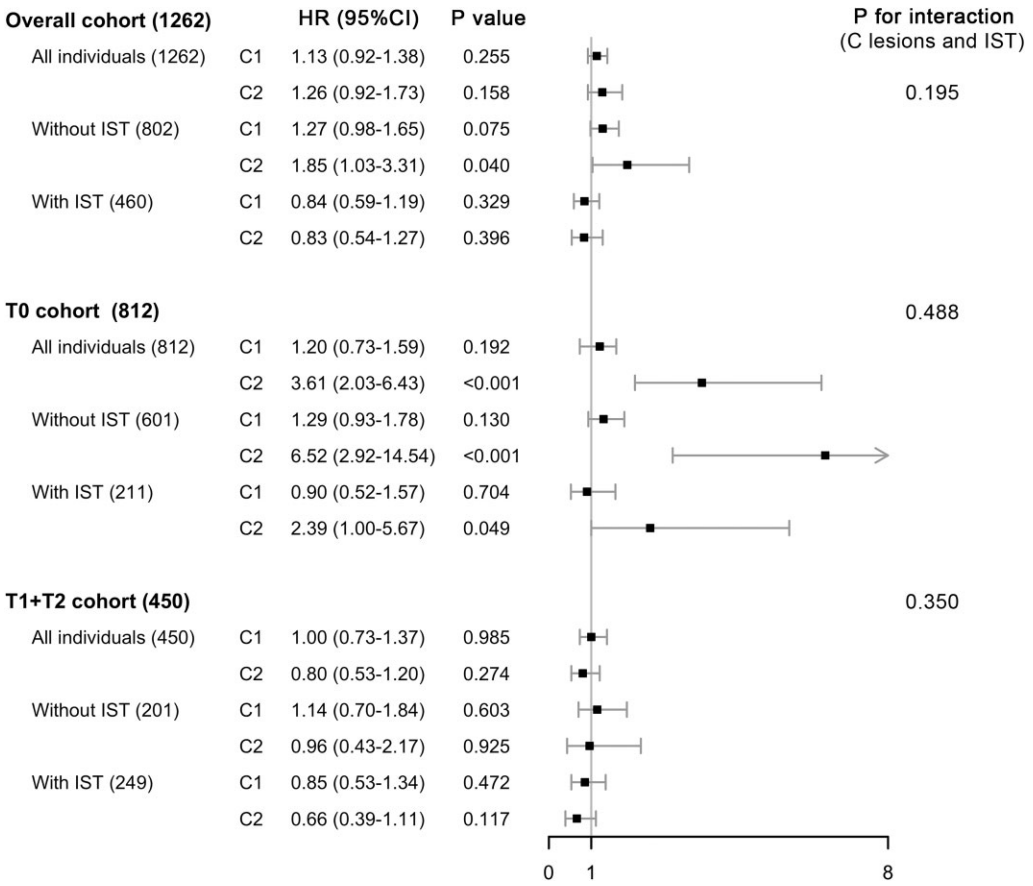


Figure 3: The effect of crescents on kidney outcomes in the overall IgAN cohort and the cohort with different T lesions by multivariate Cox regression. Composite kidney endpoint, defined by either a ≥30% reduction in the eGFR, ESKD (eGFR <15 ml/min/1.73 m^2), kidney replacement therapy for at least 6 months or kidney transplantation.

slope of eGFR decline or the proportion of ESKD and composite kidney endpoints among the three groups (Table 3).

By multivariate Cox regression analysis, IST could significantly reduce the risk of kidney outcomes only in IgAN patients with severe glomerular activity [HR 0.30 (95% CI 0.12–0.74), $P = .009$, reference to those without IST], after adjusting for age, eGFR, MAP, proteinuria at the time of biopsy and MST scores. However, IST did not reduce the risk of kidney outcomes in patients with mild or moderate glomerular activity (Fig. 4).

Effect of immunosuppressive therapy on IgAN patients with different active glomerular lesions and different degrees of chronic lesions

Due to the occult nature of IgAN, patients always present with both acute and chronic histological lesions. Therefore we further stratified according to different degrees of T lesions to evaluate the response of active glomerular lesions to IST. There was no interaction between the activity score and IST therapy in the overall cohort ($P = .057$) and T1/2 cohort ($P = .546$), although in the T0 cohort the activity score interacted with IST ($P = .025$). In the present study we investigated the response to IST of patients with different active lesions in different degrees of chronic pathological lesions by clinical experience and according to previous studies [12]. Using multivariate Cox regression analysis, IST was a more significant protective factor for kidney outcomes in patients with T0 and severe glomerular activity [HR 0.14 (95% CI 0.04–0.54), $P = .005$, reference to those without IST], whereas IST did not improve kidney outcomes in those with T1/2 lesions and severe glomerular activity [HR 1.34 (95% CI 0.16–11.23), $P = .785$, reference to those without IST] after adjusting for age, proteinuria, MAP and eGFR at biopsy and MS scores. For patients with mild or moderate severity, IST did not reduce the risk of kidney outcomes in patients with either T0 or T1/2 (Fig. 4).

Since the cohort was acquired over a 22-year period, patients who received kidney biopsies in 1994–2005 and 2006–2016 were analysed separately. There were 246 patients in the 1994–2005 group. However, among 246 patients, all patients with C2 had received IST and only 13 patients scored as severe, so further analysis cannot be done in these patients. The results of 1016 patients in the 2006–2016 group were very similar to the whole cohort. For patients with severe glomerular activity, IST reduced the risk of kidney outcomes by 67% in the overall cohort [HR 0.33 (95% CI 0.13–0.88), $P = .026$, reference to those without IST) and 86% in T0 patients [HR 0.14 (95% CI 0.03–0.71), $P = .018$, reference to those without IST].

DISCUSSION

In the present study we found that patients with C2 lesions had a 1.85 times higher risk of kidney outcomes if they did not receive immunosuppressive therapy, while for those receiving immuno-

Table 3: Clinicopathological characteristics in patients with different degrees of glomerular activity.

Characteristics	Mild ($n = 375$)	Moderate ($n = 778$)	Severe ($n = 109$)
Female, % (n)	46.1 (173)	51.3 (399)	55.0 (60)
Age (years), mean ± SD	35 ± 12	35 ± 11	36 ± 14
MAP (mmHg), mean ± SD	94 ± 11	93 ± 12	95 ± 12
Hypertension, % (n)	50.9 (191)	47.0 (366)	46.8 (51)
eGFR (ml/min/1.73 m^2), mean ± SD	87 ± 30	82 ± 30[b]	70 ± 34[a]
Proteinuria (g/24 h), median (IQR)	1.07 (0.58–2.04)	1.22 (0.66–2.31)	2.78 (1.33–4.79)[a]
Microscopic haematuria (RBCs/μl), median (IQR)	59.6 (22.7–188.8)	112.1 (43.8–290.9)	253.9 (102.3–903.1)[a]
History of macroscopic haematuria, % (n)	25.6 (56)	28.4 (221)	33.0 (36)
Pathology, % (n)			
M1	32.0 (120)[a]	44.6 (347)	40.4 (44)
S1	58.9 (221)[b]	67.5 (525)	56.0 (66)
T1, T2	19.5, 7.7 (73, 29)	26.1, 10.7 (203, 83)	39.4, 17.4 (43, 19)[a]
Follow-up			
Length of follow-up (years), median (IQR)	4.25 (2.25–7.33)	3.75 (1.98–6.75)	2.83 (1.75–5.13)[a, b]
Time-averaged proteinuria (g/24 h), median (IQR)	0.81 (0.42–1.33)	0.86 (0.50–1.43)	0.93 (0.54–2.13)[c]
Time-averaged haematuria (RBCs/μl), median (IQR)	48.4 (20.7–124.5)[a]	82.1 (31.1–175.7)	106.1 (52.0–232.6)[a]
Immunosuppressive therapy, % (n)	26.9 (101)	34.8 (271)	80.7 (88)[a]
RAS blocker, % (n)	96.8 (363)	96.7 (752)	98.3 (107)
Outcomes			
Slope eGFR (ml/min/1.73 m^2/year), mean ± SD	−2.78 ± 3.01	−3.13 ± 3.40	−3.06 ± 3.42
ESKD, % (n)	8.8 (33)	9.4 (73)	11.9 (13)
eGFR decrease ≥50%, % (n)	10.7 (40)	14.5 (113)	20.2 (22)[c]
eGFR decrease ≥30%, % (n)	33.1 (124)	36.1 (281)	35.8 (39)
Composite kidney endpoint, % (n)	33.6 (126)	36.2 (282)	37.6 (41)

[a]$P < .001$ eGFR, comparison between severe and mild or moderate group; proteinuria, comparison between severe and mild or moderate group; microscopic haematuria, comparison between each of two groups; M1, comparison between mild and moderate or severe group; T1/2, comparison between each of two groups; length of follow-up, severe group compared to mild group; time-averaged haematuria, comparison between mild and moderate or severe group; immunosuppressive therapy, comparison between each of two groups.

[b]$P < .01$ eGFR, mild group compared with moderate group; S1, mild group compared with moderate group.

[c]$P < .05$ eGFR decrease ≥50%, mild group compared with severe group; length of follow-up, severe group compared with moderate group; time-averaged proteinuria, mild group compared with severe group; time-averaged haematuria, severe group compared with moderate group.

Composite kidney endpoint, defined by either a ≥30% reduction in the eGFR, ESKD (eGFR <15 ml/min/1.73 m^2), kidney replacement therapy for at least 6 months or kidney transplantation.

suppressive therapy, the HR decreased to 0.83. When patients presented with crescents and fibrinoid necrosis or endocapillary hypercellularity lesions, IST reduced the risk of kidney outcomes by 70% in all IgAN patients and by 86% in patients with T0. However, immunosuppressive therapy did not reduce the risk of kidney outcomes in patients with T1/2 lesions. These results indicate that IgAN patients with crescents are at high risk of a kidney outcome if not treated with immunosuppression or when coexisting with other active lesions and mild chronic background lesions.

Two C scores are recommended by the Oxford classification system: C1 identifies patients at risk of a poor kidney outcome if they are not treated with immunosuppression and C2 identifies patients at high risk of a poor kidney outcome even if treated with immunosuppression. There were two important questions about the significance of crescents in IgAN. The first question was whether crescents are an independent risk factor for poor kidney outcomes and the second was whether crescents are a pathological indicator of IST. To date, several studies have confirmed the correlation between crescents and kidney prognosis, but the proportions of crescents in the glomeruli that affect kidney survival are not consistent [9, 10, 15–18]. Moreover, several studies, including the latest validation study of the Validation Study of the Oxford Classification of IgAN cohort, have shown that crescents are not significant predictors of long-term kidney prognosis [19–22]. The controversy about the prognostic value of crescents in IgAN was mainly related to different entry criteria and therapy strategies. It is supposed that IST affects the prognostic value of crescents in IgAN. This is why crescentic lesions are not included in the IgAN international prognosis calculator. In the present study we also analysed the prognostic value of crescents and found that C lesions were not a significant risk factor for kidney outcomes, which was consistent with previous validation studies [19, 20, 22]. Therefore, the most important objective of the present study was to analyse whether crescents are an indicator of the need for IST.

In a subanalysis of the STOP-IgAN trial involving 70 IgAN patients [23], IgAN patients with C1/C2 lesions who did not receive IST experienced more progression to ESKD than those with C0, whereas this was not the case in patients with IST. Peng *et al.* [10] also found that IST was apparently associated with a higher proteinuria remission rate in patients with C2 lesions. In the present study, we found that both C1 and C2 lesions, especially C2 lesions, could significantly increase the risk of kidney outcomes in patients without IST and the risk decreased in those who received IST. These results were inconsistent with the results of Haas et al. [7] regarding the significance of C2 lesions. Therefore we further analysed the possible reason for the differences from previous studies.

IgAN is a disease with significant pathological heterogeneity. Crescents can be a concomitant occurrence with almost all kinds of pathological lesions in IgAN and can present in different degrees of chronic tubular and interstitial lesions, which is the strongest factor to predict kidney outcomes in IgAN. We assumed that T lesions might be a significant bias influencing

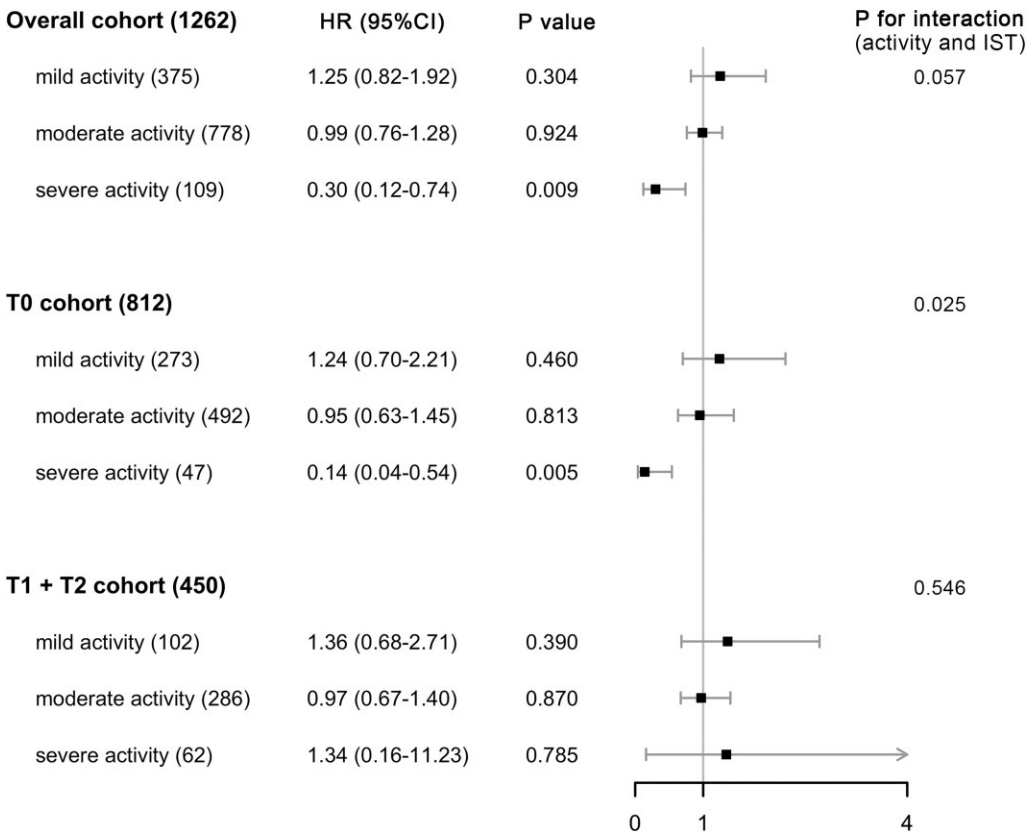


Figure 4: The effect of immunosuppressive therapy on IgAN patients with different activity scores and chronic pathological lesions by multivariate Cox regression model. Composite kidney endpoint, defined by either a ≥30% reduction in the eGFR, ESKD (eGFR <15 ml/min/1.73 m^2), kidney replacement therapy for at least 6 months or kidney transplantation.

the therapeutic significance of crescents. In the present study we further divided all IgAN patients into two groups, including patients with T0 and patients with T1/2, and analysed the significance of crescents separately. Interestingly, the predictive value of C2 but not C1 lesions was ≈6.5 times higher in patients with T0 who did not receive IST, and the HR decreased to 2.39 in patients with T0 who received IST. In addition, we also analysed the significance of C1/2 lesions in patients with an eGFR >60 ml/min/1.73 m^2 and the results were very similar to those in patients with T0. Patients with C2 but not C1 lesions who did not receive IST had an ≈3 times higher risk for kidney outcomes and the HR decreased to 0.92 in those who received IST. However, in patients with T1/2 lesions or an eGFR <60 ml/min/1.73 m^2, neither C1 nor C2 lesions were significant risk factors for kidney outcomes regardless of whether IST was performed (Supplementary Table S2). Severe chronic tubular and interstitial lesions and a low eGFR at the time of kidney biopsy were more important in predicting kidney outcomes. Crescents, especially C2 lesions, were a significant risk factor for poor kidney outcomes in patients with mild T lesions or preserved kidney function, and IST might provide greater benefits for patients with mild T lesions or preserved kidney function.

It has been confirmed that T lesions are the most powerful pathological lesions to indicate kidney outcomes, and severe T lesions represent the late stage of IgAN and high levels of serum creatinine (SCr) [14]. In IgAN, there is a 'point of no return', which indicates that patients with SCr levels >3 mg/dl are thought to be non-responsive to all treatment strategies [24, 25]. For IgAN patients with crescents, when the SCr level is >600 μmol/L, these patients cannot avoid dialysis during a follow-up of 1 year. Therefore, T1/2 lesions, especially T2 lesions, might weaken the prognostic value of other pathological parameters. Compared with the pathological characteristics of the cohort in studies from Katafuchi *et al.* [26] and Walsh *et al.* [27], the common difference from our cohort was the higher fractions of T lesions. These chronic pathological lesions interact with active lesions such as crescents, which may interfere with the effect of crescents on the prognosis of IgAN. Sehoon *et al.* [9] found that the risk of poor kidney outcomes of C2 lesions increased significantly in patients with mild interstitial fibrosis and tubular atrophy, but the study did not further evaluate the response to treatment due to the small number of patients with C2 lesions (1.8%). In the present study, we found that IST could reduce the risk of poor kidney outcomes of patients with C2 lesions by 49% in all patients and by 76% in patients with T0, even if the *P*-value was borderline statistically significant. From the results of the present study, more attention should be given by nephrologists to the pathological background of each patient when C2 lesions are present, and IST is suggested for those without severe chronic histological lesions.

As mentioned before, crescents always coexist with other active lesions, including fibrinoid necrosis and endocapillary hypercellularity lesions in IgAN, and can present as different background chronic pathological lesions. A recent study by Itami *et al.* [12] proposed a novel classification based on the Oxford score, which used an activity score of 0–4 (M1 + E1 + S1 + C1/2)

and T scores (T0 or T1/2), and they found that patients who presented with high activity could benefit from immunosuppression, especially among those with mild chronic lesions (T0). A subsequent commentary [28] suggested that the use of immunosuppressive agents in IgAN should consider both active and chronic lesions. In the present study, we found that immunosuppressive therapy could reduce the risk of poor kidney outcomes by 70% in patients with severe glomerular activity, which indicates the presence of crescents and at least one other active lesion, and the risk was further reduced by 86% in patients with T0. However, the risk did not decrease in patients with T1/2 lesions and the benefit of immunosuppression should be fully considered in these patients. The results of the present study suggest that nephrologists should consider not only chronic background pathological lesions but also other active lesions when making treatment decisions for crescents in IgAN. The recently published Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study found a benefit of steroids in IgAN [29]; however, the side effects of steroids, especially those of full doses of steroids, should be taken seriously. Our results provide suggestions to nephrologists that when IgAN patients present with both crescents and T1 or T2 lesions, especially T2 lesions, immunosuppressive therapy should be considered very carefully.

In the present study, C1 lesions were not as significant a risk factor as that of C2 lesions, which could indicate possible benefits from immunosuppressive therapy. The median proportion of crescents in the glomeruli in our cohort was 5%; 117 patients had crescents in <5% of the glomeruli, 295 patients had crescents in <10% and 448 patients had crescents in <15%. In a study of 538 patients with IgAN from China, Zhang *et al.* [18] found that there was no difference in prognosis between patients with crescents in <5% of the glomeruli and those without crescents. However, in the remaining groups, the kidney prognosis worsened as the proportion of crescents increased. Therefore we speculated that patients with a small percentage of crescents would not benefit from aggressive treatment, and this may affect the response to immunosuppression in the C1 group. It has been reported that a proportion of glomerulosclerosis >25% is correlated with a decreased kidney survival rate in IgAN patients [10]. Thus we further calculated the C scores based on the proportion of crescents in the non-sclerotic glomeruli, and 54 patients who used to have crescents in <25% of the glomeruli and scored as C1 were classified into C2 group. We found that the presence of crescents in ≥25% of the non-sclerotic glomeruli was an independent risk factor for poor kidney outcomes in all individuals and patients who did not receive IST were at higher risk, which was significantly reduced by IST (Supplementary Table S3). These results suggest that patients with crescents could benefit from immunosuppressive therapy after the crescents reach a certain percentage, and this cut-off may be <25%. Multicentre studies including more patients with crescents are needed to determine the proper cut-off of the proportion of crescents in patients who should be treated with IST.

The present study has some limitations. First, this was a single-centre, retrospective study. Multicentre, prospective, randomized controlled studies, such as the TESTING study, are more objective for evaluating the prognosis of crescents and response to immunosuppressive therapy in IgAN. Second, the pathological characteristics of IgAN were focal and heterogeneous, and the proportion of crescents might change with different numbers of glomeruli in renal biopsies. Special biomarker staining, such as urine soluble CD163, which was associated with crescents and fibrinoid necrosis lesions in lupus and antibody-associated systemic vasculitis or complement component C4d [30] or $CD68^+$ [31] in renal biopsy samples, is needed to provide a clear description of the pathological presentation of patients for whom immunosuppressive therapy may benefit. Moreover, crescents are more commonly reported in Asians than Europeans. In the present study, an overall 56.3% of patients had a C score, which was much higher than that in Caucasian patients, so the results in the present study need to be validated in other ethnic IgAN patients.

CONCLUSION

In conclusion, our study suggested that immunosuppressive therapy could reduce the risk for poor kidney outcomes in IgAN patients with crescents, especially when these patients presented with at least one other active lesion, including fibrinoid necrosis and endocapillary hypercellularity lesions, or mild chronic tubular and interstitial lesions.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

The study was approved by the ethics committee of Peking University First Hospital (2013[548]) and was executed in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from each patient and a copy of the written consent is available upon request.

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AUTHORS' CONTRIBUTIONS

Y.G. was responsible for data collection, statistical analysis and manuscript writing. X.Z., J.L., L.L. and L.Z. were responsible for patients' follow-up. S.W. was responsible for pathology scores. S.S. designed and supervised the study and revised it critically. H.Z. was responsible for manuscript review. All authors provided final manuscript approval.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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