scientific reports

Check for updates

OPEN

Clinical features, pathological characteristics, and prognosis of patients with IgA nephropathy complicated with nephrotic syndrome

Li Tan[1,2,3], Lu-Hua Jin[1,2,3], Yi-Qin Wang[1,2], Wei Chen[1,2] & Qiong Wen[1,2]✉

Nephrotic syndrome (NS) occurs in 5-15% of patients with IgA nephropathy (IgAN), resulting in poorer long-term outcomes compared to those without NS. Clinical features and renal prognosis for patients with both NS and IgAN across different kidney pathologies have not been fully elucidated. This study included patients with primary IgAN through renal biopsy at the First Affiliated Hospital of Sun Yat-sen University from January 2001 to November 2021 presenting with NS. Renal endpoint was defined as a 50% decrease in estimated glomerular filtration rate or progression to end-stage renal disease. A total of 207 patients with IgAN and NS were categorized into four pathological groups: IgAN with mesangial proliferative glomerulonephritis (IgAN-MsPGN) (*n* = 150), IgAN with minimal change disease (IgAN-MCD) (*n* = 49), IgAN with membranous nephropathy (IgAN-MN) (*n* = 7), and IgAN with membranoproliferative glomerulonephritis (IgAN-MPGN) (*n* = 1). Compared to the IgAN-MsPGN group, the IgAN-MCD group consisted of more males, had a younger average age, lower blood pressure, a lower prevalence of hematuria, and lower serum albumin and creatinine levels, whereas the IgAN-MN group was characterized by an older average age and lower serum creatinine levels. The IgAN-MCD group exhibited the mildest pathological changes among the groups. Of all patients, 133 were followed for an average follow-up period of 52.07 ± 44.04 months. Thirty-seven patients (27.8%) reached the renal endpoint. The IgAN-MCD group showed a higher rate of proteinuria remission and a better renal prognosis than the IgAN-MsPGN group. In conclusions, significant differences in clinicopathological features and long-term prognosis were observed among NS-IgAN patients with varying pathological phenotypes.

Keywords IgA nephropathy, Nephrotic syndrome, Pathological classification corticosteroid, Renal prognosis

IgA nephropathy (IgAN) is one of the most common glomerulonephritis worldwide. A systematic review involving studies from different countries showed that the incidence of IgAN was at least 25 cases per million population[1]. Clinical manifestations of IgAN include asymptomatic hematuria or proteinuria, acute or chronic nephritis, rapidly progressive glomerulonephritis, and/or nephrotic syndrome. The treatment for and prognosis of IgAN depends on the presentations and varies according to the underlying pathogenesis and pathological features. Approximately 27% of patients with IgAN have slow but progressive worsening of kidney function that leads to end-stage kidney disease (ESKD) or at least 50% estimated glomerular filtration rate (eGFR) decline within ten years[2]. A recent cohort study suggested that among those with IgAN and a urinary protein-to-creatinine ratio (UPCR) higher than 1.76 g/g, the risk of developing ESKD within ten years was about 85%[3]. This suggests that patients with IgAN patients and nephrotic range proteinuria are at an even higher risk of ESKD progression.

Patients with IgAN rarely present with nephrotic syndrome (NS). Previous research indicates that the prevalence of NS in individuals with IgAN ranges from 5 to 15%[4–7]. The presence of substantial proteinuria and

[1]Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, 58 Zhongshan Road II, Guangzhou 510080, China. [2]NHC Key Laboratory of Clinical Nephrology, Guangdong Provincial Key Laboratory of Nephrology, Sun Yat-Sen University, Guangzhou 510080, China. [3]These authors contributed equally: Li Tan and Lu-Hua Jin. ✉email: wenqiong@mail.sysu.edu.cn

diminished renal function at the time of diagnosis places NS-IgAN patients at an elevated risk of developing ESKD compared to their non-NS counterparts. Specifically, a study demonstrated that the 5-year renal survival rates for patients with and without NS were 73.1% and 87.8% ($P < 0.001$), respectively[6], indicating a significant difference ($P < 0.001$). The 2021 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend treating patients with NS-IgAN, whose biopsy results align with minimal change disease (MCD), following the guidelines for MCD. Additionally, patients with NS-IgAN exhibiting features of coexistent mesangial proliferative glomerulonephritis are advised to be managed as those at a heightened risk of progressing to chronic kidney disease (CKD[8]). Consequently, accurate renal pathology identification via biopsy in NS-IgAN patients is crucial for directing treatment and predicting prognosis. Prior studies have concentrated on delineating the clinical features and renal outcomes between IgAN patients with and without NS. However, few reports addressed the associations between kidney pathological classification and kidney function decline among NS-IgAN patients. Our study thus aimed to explore the clinical-pathological characteristics and their relationship with kidney prognosis among patients with NS-IgAN.

Materials and methods

Patient population

We retrospectively screened 4963 patients with biopsy-proven primary IgAN at the First Affiliated Hospital of Sun Yat-sen University between January 2001 and December 2021. The inclusion criteria were as follows: (1) biopsy-proven primary IgAN; (2) massive proteinuria (> 3.5 g/d) and hypoalbuminemia (lower than 30 g/d); and (3) age > 14 years old. Exclusion criteria were as follows: (1) prior history of systemic diseases such as malignancies or cirrhosis; (2) secondary IgAN, such as allergic purpura nephritis, systemic lupus erythematosus, myeloma-related diseases, hypertensive kidney damages, diabetic nephropathy, hepatitis B related nephropathy, cirrhosis related nephropathy; or (3) the number of glomeruli under light microscopy lower than 8, or missing or poor quality of electron microscopy results.

Data collection

All clinical data was obtained during kidney biopsy, including age, gender, body mass index (BMI), comorbidities such as hypertension, diabetes mellitus and cardiovascular disease (CVD); systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), 24-h urinary protein, hematuria, hemoglobin (Hb), serum albumin (ALB), serum creatinine (Scr), uric acid (UA), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-c), low-density lipoprotein cholesterol (LDL-c) and complement factor 3 (C3).

Definitions

We defined NS as the presence of massive proteinuria (24-hour urinary protein > 3.5 g) and hypoalbuminemia (ALB < 30 g/L) with or without edema and hyperlipidemia. We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. We identified ESKD as having an eGFR < 15 ml/min per 1.73 m^2. Hypertension was diagnosed if patients had an SBP ≥ 140mmHg and/or DBP ≥ 90mmHg. The diagnostic criteria for diabetes mellitus were as follows: having typical diabetes-associated symptoms combined with random blood glucose ≥ 11.1 mmol/L, fasting blood glucose ≥ 7.0 mmol/L, an oral glucose tolerance test (OGTT) 2 h blood glucose ≥ 11.1 mmol/L, or glycated hemoglobin (HbAlc) ≥ 6.5%. CVD was identified if patients had myocardial infarction, non-myocardial infarction, acute coronary syndrome, stroke, or acute decompensated heart failure. We obtained MAP using the formula "DBP+ (SBP- DBP)/3". To identify microscopic hematuria, we centrifugated patients' morning urine samples and retrieved precipitation; if the average number of microscopic red blood cells per high-power field exceeded 3, microscopic hematuria was diagnosed. The glomerulosclerosis ratio was calculated based on the proportion of glomeruli with sclerosis and atrophy relative to the total glomerular number.

Renal pathology evaluation

Kidney pathology was assessed using the IgAN Oxford classification as follows: (1) A mesangial score of < 0.5 categorized as M0, and > 0.5 if M1; (2) Endocapillary hypercellularity classified as absent E0 or present if E1; (3) Segmental glomerulosclerosis identified as absent S0 or present S1, with the S1 category further differentiated based on the presence or absence of podocyte hypertrophy/tip lesions; (4) Tubular atrophy/interstitial fibrosis quantified as ≤ 25% if T0, between 26 and 50% T1, or > 50% T2; (5) Cellular/fibrocellular crescents classified as absent if C0, present in at least one glomerulus if C1, or in more than 25% of glomeruli if C2.

Patients with NS-IgAN patients were divided into four categories based on their light microscopy, immunofluorescence, and electron microscopy findings, including IgAN-minimal change disease (MCD), IgAN-membranous nephropathy (MN), IgAN-membranoproliferative glomerulonephritis (IgAN-MPGN), and IgAN-mesangial proliferative glomerulonephritis (IgAN-MsPGN). Each pathological type must meet the typical pathological manifestations of IgAN: predominant or codominant IgA-containing immune deposits, usually with complement C3 co-deposits and with variable presence of IgG and/or IgM[9]. IgAN-MCD required the presence of minimal glomerular changes under light microscopy and diffuse effacement of foot processes (at least 50% of the capillary surface area) under electron microscopy, with mild mesangial hypercellularity but without endocapillary proliferation, segmental glomerulosclerosis, interstitial fibrosis, tubular atrophy, or cellular crescents[10]. IgAN-MN was recognized based on IgG and/or C3 deposition in glomerular capillary walls and subepithelial electron-dense deposits[11]. IgAN-MPGN was diagnosed if pathologies revealed severe diffuse mesangial proliferation and matrix expansion under light microscopy, resulting in the insertion of a matrix between the glomerular basement membrane and endothelial cells, termed the "double track" capillary loop. MPGN also manifested under immunofluorescence staining granular deposition of IgG and C3 in mesangial and capillary walls, with electron-dense deposits in mesangial and subendothelial zones[12]. IgAN-MsPGN was

identified based on the diffuse proliferation of glomerular mesangial cells and mesangial matrix expansion under light microscopy, accompanied by electron-dense deposits in mesangial areas under electron microscopy[13]. Renal biopsy slides were evaluated by two pathologists at our center, and the agreement rate between the two pathologists was 90%. If the two pathologists had inconsistent judgments, they would discuss them and give a mutually agreed diagnosis.

Treatment and response documentation

Patients were provided supportive care by prescribing maximum tolerable doses of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs). Oral corticosteroid therapy (OCT) involved administering 0.5–1 mg/kg of prednisone orally daily, not exceeding 60 mg/day, with subsequent gradual dose reductions based on the patient's condition and tolerance. Corticosteroid pulse therapy (CPT) entailed administering intravenous methylprednisolone at 0.5 g/day for three days to treat cellular crescentic lesions, followed by a maintenance regimen of oral prednisone at 0.5-1 mg/kg daily, up to a maximum of 60 mg/day.[14] Modified POZZI therapy[15] included administering 0.5 g/day of methylprednisolone intravenously for three consecutive days in the first, third, and fifth months, coupled with oral prednisone at 0.5 mg/kg/day for six months. After six months, the dosage of oral corticosteroids was gradually reduced until completely discontinued. Immunosuppressive treatments included mycophenolate mofetil, cyclophosphamide, calcineurin inhibitors, imidazoribine, leflunomide, and others.

Treatment response could be divided into complete proteinuria remission (CR), partial proteinuria remission (PR), and no proteinuria remission (NR). CR was defined as 24-h urinary protein less than 200 mg/day. PR was defined as proteinuria declining to less than 50% of baseline by 24-h urinary protein and less than 1 g/day. NR was defined if patients failed to meet CR and PR standards[16]. Relief of proteinuria (RP) referred to the presence of CR or PR. Patients needed at least a 50% decrease in eGFR for renal endpoint development or reached ESKD.

Statistical analysis

Statistical analyses were performed using SPSS software (Version 26). Quantitative data that followed a normal or near-normal distribution were presented as means ± standard deviations (SDs), with independent sample t-tests utilized to compare means between two samples. Categorical data were represented as counts or percentages, with group comparisons conducted using χ^2 tests. Nonparametric tests, such as rank sum tests, were employed to compare data that did not adhere to a normal distribution. Kaplan-Meier survival curves were constructed to evaluate renal survival rates between groups, and Log Rank tests were applied for comparisons. COX regression analyses explored risk factors associated with poor renal prognosis. A *P*-value is statistically significant if $P < 0.05$.

Results

Overall characteristics of patients with NS-IgAN

From January 2001 to December 2021, 4963 patients had biopsy-proven primary IgAN identified from the Nephrology Department of the First Affiliated Hospital of Sun Yat-sen University. Among them, 276 (5.6%) presented with NS. Totally 207 patients with NS-IgAN met the inclusion and exclusion criteria and could be divided into four categories (IgAN-MsPGN, $n = 150$, 72.5%; IgAN-MCD, $n = 49$, 23. 7%; IgAN-MN, $n = 7$, 3.4%; and IgAN-MPGN, $n = 1$, 0.5%) (Fig. 1).

As shown in Table 1, the mean age of these patients with NS-IgAN was 31.13 ± 12.84 years, and 110 (53.1%) were males. Microscopic hematuria was noted in 161 (77.8%) patients. Their 24-h urinary protein values were 6.42 ± 3.68 g, and the baseline eGFR was 68.71 ± 45.46 mL/min/1.73 m^2. Among all, 29 (14.0%) had an eGFR < 15 mL/min/1.73m^2 at baseline. Table 1 also showed that the Oxford classification components (M, E, S, T, and C) were present in patients with NS-IgAN. This finding aligns with earlier research reports[17], indicating that complement C3 deposition was common (63.3%) in patients with NS-IgAN, while C1q deposition was less frequent (12.6%).

Among all, 66.2% of patients received ACEis or ARBs, whereas 71.8%, 22.1%, and 1.5% chose OCT, CPT, and the modified POZZI regimen as the initial treatment. In addition, 19.5% of patients received immunosuppressants. At follow-up, the proportion of microscopic hematuria in patients with NS-IgAN decreased compared to prior treatments (before vs. after, 77.8% vs. 54.2%). We recorded proteinuria levels at one year of follow-up among 99 patients with NS-IgAN; 67.7% achieved RP after treatment. A total of 133 patients had renal endpoint data available, with an average follow-up duration of 52.07 ± 44.04 months. Thirty-seven (27.8%) developed the renal endpoint (Table 2).

Comparisons between different pathological subtypes

Table 1 showed that among the 150 patients with IgAN-MsPGN, 67 (44.7%) were male. Patients with IgAN-MCD exhibited a higher proportion of males but lower ages, blood pressures, ALB levels, and Scr levels, and they had a lower incidence of microscopic hematuria than those with IgAN-MsPGN. The two groups had no significant difference in 24-h urinary protein levels. Patients with IgAN-MsPGN exhibited eGFR levels across all kidney function stages, whereas 98.0% of those with IgAN-MCD had an eGFR ≥ 60 mL/min/1.73 m^2, with only one patient having an eGFR < 44 mL/min/1.73m^2 recovering who recovered after treatment. Compared to those with IgAN-MsPGN, patients with IgAN-MN were older and had lower Scr levels. No significant differences were observed in the proportion of males, blood pressure, hematuria, 24-h proteinuria, or baseline eGFR between these two groups. The single patient with IgAN-MPGN was a 27-year-old male with a baseline eGFR of 38.28 mL/min/1.73 m^2 and a 24-h urinary protein level of 8.05 g.

Patients with IgAN-MCD exhibited the least severe pathological features compared to those with IgAN-MsPGN. The incidence of S1 was significantly higher in patients with IgAN-MsPGN than in those with IgAN-MN. The two groups had no notable differences regarding M1, E1, T1-2, C1-2 scores, C3 and C1q deposition rates,

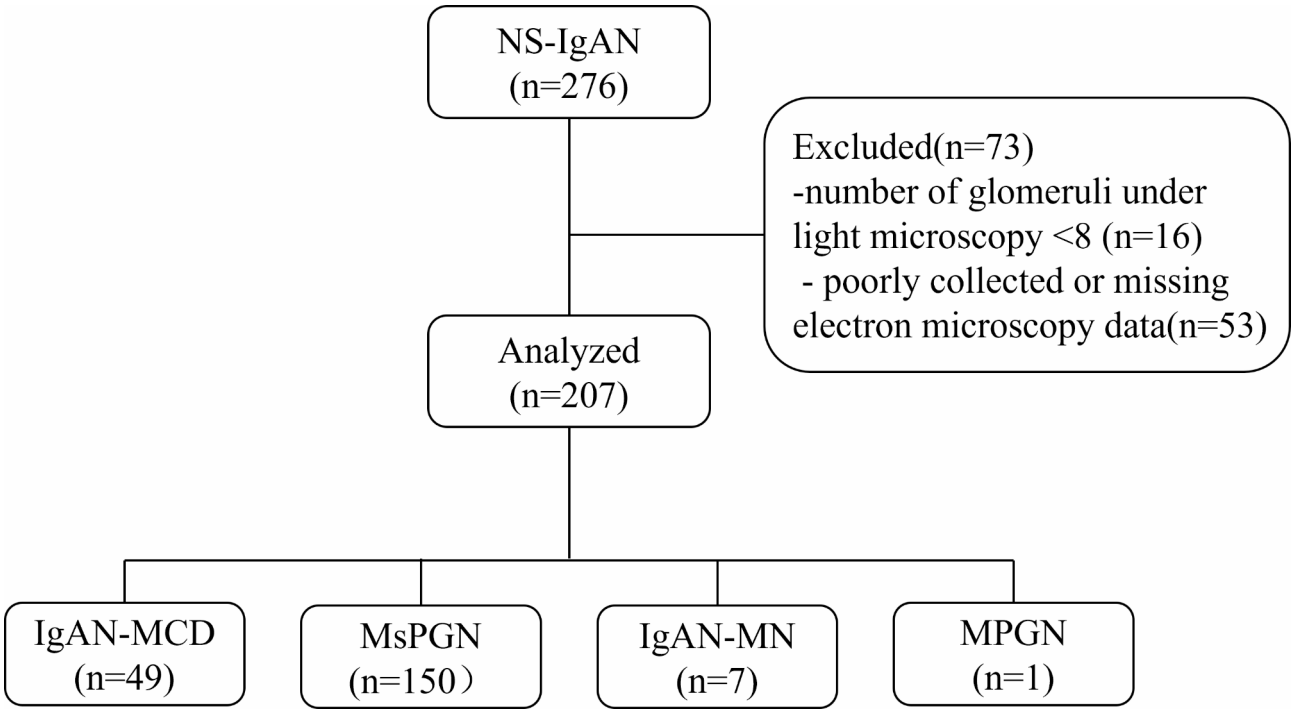

Fig. 1. Flow diagram of patient selection. From January 2001 through December 2021, IgA nephropathy was diagnosed in 4963 patients, and 276 presented with nephrotic syndrome. Among them, 207 patients were enrolled. *NS-IgAN* immunoglobulin (Ig)A nephropathy with nephrotic syndrome, *IgAN-MCD* IgAN with minimal change disease, *IgAN-MsPGN* IgAN with mesangial proliferative glomerulonephritis, *IgAN-MN* IgAN with membranous nephropathy, *IgAN-MPGN* IgAN with membranoproliferative glomerulonephritis.

and the proportion of glomerulosclerosis. The singular patient with IgAN-MPGN had an Oxford classification of M1E1S1T1C1, exhibited 2 + C3 deposition but lacked C1q deposition, and showed a glomerulosclerosis proportion of 0.35.

Table 2 showed no significant difference in the proportion of patients receiving ACEis, ARBs, or immunosuppressants between the IgAN-MsPGN, IgAN-MN, and IgAN-MCD groups. Patients with IgAN-MCD all chose to receive OCT, while 31.4% of patients with IgAN-MsPGN and 28.6% with IgAN-MN received CPT for managing crescentic lesions. Two patients with IgAN-MsPGN received the modified POZZI regimen. At follow-up, the percentage of microscopic hematuria decreased in all three groups compared to before treatment. However, the percentage of microscopic hematuria in the patients with the IgAN-MsPGN group remained higher than in the other two groups. Regarding prognosis, the RP and renal prognosis rates of patients with IgAN-MCD and those with IgAN-MN were better than those of patients with IgAN-MsPGN. Only one patient with IgAN-MPGN initially received ACEis and oral steroids. However, he did not achieve proteinuria remission while developing renal endpoint at 45 months of follow-up. For this patient, we excluded the possibility of other causes of secondary kidney diseases at the time of the kidney biopsy. He currently receives regular follow-ups in this institute and has not shown evidence of secondary kidney disease.

Comparisons between patients with or without ACEi/ARB therapy

Of the 133 patients with NS-IgAN with follow-up data available, 88 received ACEi/ARB therapies. Some patients did not receive this therapy because their serum creatinine levels were too high at presentation, or their baseline blood pressure was too low to tolerate ACEi/ARB. There were no significant differences in gender, age, comorbidities, blood pressure and proteinuria levels, and pathologic changes between patients treated without and with ACEi/ARB. Serum creatinine levels were significantly lower in patients treated with ACEi/ARB than those without (Table 3).

A higher proportion of patients treated with ACEi/ARB were treated with CPT and immunosuppressants than those without. Patients treated with ACEi/ARB had significantly longer follow-up durations. There was no significant difference between the two groups regarding the proportion of microscopic hematuria and proteinuria resolution at follow-up. Patients who did not receive ACEi/ARB were more likely to develop renal endpoints than those who did (Table 4).

Comparisons between patients with different renal function

Table 3 showed that patients with an eGFR ≥ 60 had significantly lower age, blood pressure, uric acid levels, and hematuria than those with an eGFR < 60. According to the Oxford classification, patients with an eGFR < 60 had more severe pathological changes than those with an eGFR ≥ 60.

	NS-IgAN ($n=207$)	IgAN-MsPGN ($n=150$)	IgAN-MCD ($n=49$)	IgAN-MN ($n=7$)
Male (%)	110 (53.1)	67 (44.7)*	38 (77.6)	4 (57.1)
Age, years	31.13 ± 12.84	32.79 ± 12.67*†	24.41 ± 9.92§	43.14 ± 16.79
BMI, kg/m^2	22.90 ± 3.24	22.95 ± 3.48	22.75 ± 3.04	23.0 ± 2.72
Hypertension (%)	101 (48.8)	89 (59.3)*	10 (20.4)	2 (28.6)
Diabetes mellitus (%)	10 (4.8)	8 (5.3)	2 (4.1)	–
CVD (%)	1 (0.5)	1 (0.7)	–	–
SBP, mmHg	132.82 ± 20.87	137.56 ± 20.82*	118.88 ± 15.34	130.57 ± 11.0
DBP, mmHg	83.54 ± 14.42	86.33 ± 14.56*	75.82 ± 11.4	79.86 ± 10.29
MAP, mmHg	99.97 ± 15.37	103.4 ± 15.37*	90.17 ± 11.54	96.76 ± 7.72
Hb, g/L	121.87 ± 28.68	112.85 ± 24.86*	150.67 ± 21.35§	115.04 ± 18.99
UA, μmol/L	429.43 ± 125.06	438.17 ± 130.19	403.86 ± 113.98	425.73 ± 68.52
TC, mmol/L	7.78 ± 2.98	7.09 ± 2.47*	10.12 ± 3.33§	6.46 ± 2.38
TG, mmol/L	2.24 ± 1.32	2.26 ± 1.37	2.23 ± 1.26	1.93 ± 0.73
LDL-c, mmol/L	4.91 ± 2.26	4.37 ± 1.86*	6.69 ± 2.57§	4.19 ± 1.65
HDL-c, mmol/L	1.45 ± 0.52	1.36 ± 0.45*	1.72 ± 0.64	1.39 ± 0.47
Hematuria (%)	161 (77.8)	135 (90.0)*	20 (40.8)	5 (71.4)
24-h proteinuria, g/d	6.42 ± 3.68	6.16 ± 3.51	7.17 ± 4.28	6.52 ± 2.03
ALB, g/L	24.04 ± 5.63	25.47 ± 5.15*	19.68 ± 5.08	23.56 ± 4.15
Serum C3, g/L	0.99 ± 0.25	0.96 ± 0.26*	1.10 ± 0.19	0.96 ± 0.13
Scr, μmol/L	208.92 ± 246.92	255.89 ± 275.08*†	79.35 ± 29.18	110.86 ± 61.87
eGFR (ml/min/1.73m^2)	68.71 ± 45.46	53.36 ± 39.75*	115.31 ± 29.72§	75.77 ± 28.21
eGFR stage				
≥ 90 (%)	71 (34.3)	30 (20)	39 (79.6)	2 (28.5)
60–89 (%)	39 (18.8)	26 (17.33)	9 (18.4)	4 (57.14)
45–59 (%)	20 (9.7)	20 (14.67)	–	–
30–44 (%)	21 (10.1)	19 (12.67)	1 (2.0)	–
15–29 (%)	27 (13.0)	26 (17.33)	–	1 (14.29)
< 15 (%)	29 (14.0)	29 (19.33)	–	–
M1 (%)	166 (80.2)	128 (85.3)*	30 (61.2)§	7 (100)
E1 (%)	51 (24.6)	46 (30.7)*	–§	4 (57.1)
S1 (%)	93 (44.9)	91 (60.7)*†	–§	1 (14.3)
T1-2 (%)	99 (47.8)	96 (64.0)*	–§	2 (28.6)
C1-2 (%)	117 (56.5)	112 (74.7)*	–§	3 (42.9)
C3 deposition (%)	131 (63.3)	113 (75.3)*	12 (24.5)§	5 (71.4)
C1q deposition (%)	26 (12.6)	20 (13.3)	6 (12.2)	–
Glomerulosclerosis proportion	0.26 ± 0.27	0.34 ± 0.27*	0.02 ± 0.07	0.16 ± 0.22

Table 1. Clinicopathological data of patients with NS-IgAN and comparisons between different pathological subtypes. The only one patient with IgAN-MPGN was a 27 years-old male, with a baseline serum creatinine of 200 μmol/L, estimated glomerular filtration rate (eGFR) of 38.28 mL/min/1.73 m^2, serum albumin of 26 g/L and a 24-hour urinary protein level of 8.05 g. The Oxford classification of the only IgAN-MPGN patient was M1E1S1T1C1, the glomerular C3 deposition was 2+, but C1q deposition was negative, and the glomerulosclerosis proportion was 0.35. *NS-IgAN* immunoglobulin (Ig)A nephropathy with nephrotic syndrome; IgAN-MsPGN, IgAN with mesangial proliferative glomerulonephritis, *IgAN-MCD* IgAN with minimal change disease; IgAN-MN, IgAN with membranous nephropathy, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *Hb* hemoglobin, *UA* uric acid, *TC* total cholesterol, *TG* triglyceride (TG), *HDL-c* high-density lipoprotein, *LDL-c* low-density lipoprotein cholesterol, *ALB* serum albumin, *C3* complement factor 3, *Scr* serum creatinine, *eGFR* estimated glomerular filtration rate, *M* mesangial hypercellularity, *E* endocapillary proliferation, *S* segmental sclerosis or adhesion, *T* tubular atrophy/interstitial fibrosis, *C* crescents, *C3* complement factor 3, *C1q* complement factor 1q. *Comparison between patients with IgAN-MCD and IgAN-MsPGN, $P<0.05$. †Comparison between patients with IgAN-MN and IgAN-MsPGN, $P<0.05$. §Comparison between patients with MN-IgAN and IgAN-MCD, $P<0.05$.

Table 4 showed no significant difference between different eGFR groups regarding the proportion of patients receiving ACEi/ARB and immunosuppressants. Compared with patients with an eGFR < 60, those with an eGFR ≥ 60 were more likely to receive OCT but less likely to receive CPT. Patients with an eGFR ≥ 60 had a longer follow-up duration and were more likely to have proteinuria improvement than those with an eGFR < 60,

	NS-IgAN ($n=133$)	IgAN-MsPGN ($n=88$)	IgAN-MCD ($n=37$)	IgAN-MN ($n=7$)
ACEi/ARB (%)	88 (66.2)	58 (65.9)	23 (62.2)	6 (85.7)
SGLT-2i (%)	–	–	–	–
OCT (%)	94 (71.8)	51 (59.3)*	37 (100)§	5 (71.4)
CPT (%)	29 (22.1)	27 (31.4)*	–§	2 (28.6)
Modified POZZI therapy (%)	2 (1.5)	2 (2.3)*	–§	–
Immunosuppressant (%)	26 (19.5)	15 (17.0)	9 (24.3)	2 (28.6)
Follow-up time (months)	52.07 ± 44.04	45.66 ± 40.26*	63.68 ± 52.38	72.29 ± 27.92
Hematuria (%)	45 (54.2)	39 (67.2)*	4 (20.0)	1 (25.0)
Proteinuria remission (%)	67 (67.7)	39 (55.7)*	23 (95.8)	5 (100)
Renal endpoint event (%)	37 (27.8)	36 (40.9)*†	–	–

Table 2. Treatment and prognosis of patients with NS-IgAN and comparisons between different pathological subtypes. *NS-IgAN* immunoglobulin (Ig)A nephropathy with nephrotic syndrome, *IgAN-MsPGN* IgAN with mesangial proliferative glomerulonephritis, *IgAN-MCD* IgAN with minimal change disease, *IgAN-MN* IgAN with membranous nephropathy, *ACEis* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *SGLT-2i* sodium-dependent glucose transporters 2 inhibitors, *OCT* oral corticosteroid therapy, *CPT* corticosteroid pulse therapy. *Comparison between patients with IgAN-MCD and IgAN-MsPGN, $P<0.05$. †Comparison between patients with IgAN-MN and IgAN-MsPGN, $P<0.05$. §Comparison between patients with MN-IgAN and IgAN-MCD, $P<0.05$.

whereas the proportion of having microscopic hematuria and developing renal endpoints at follow-up was lower in those with an eGFR ≥ 60.

Analysis of renal endpoints

Univariate COX regression analysis (Table 5) indicated that several factors were associated with a significantly poorer renal prognosis in patients with NS-IgAN. These factors included higher MAP (hazard ratio (HR) 1.04, $P<0.001$), lower Hb (HR 0.96, $P<0.001$), higher UA (HR 1.01, $P<0.001$) and ALB (HR 1.16, $P=0.001$) and eGFR (HR 0.95, $P<0.001$). The presence of Oxford classification T1-2 (HR 15.98, $P<0.001$), C1-2 (HR 15.47, $P<0.001$), and a higher proportion of C3 deposition (HR 4.65, $P=0.004$) were also linked to worse outcomes. In addition, the lack of ACEi/ARB treatment (HR 0.39, $P=0.004$) was associated with a worse renal outcome.

Upon further analysis through multivariate COX regression, crescentic lesions (HR 5.71, $P=0.025$) emerged as a significant independent risk factor for a poorer renal prognosis in NS-IgAN patients, whereas eGFR (HR 0.98, $P=0.010$) and ACEi/ARB treatments (HR 0.31, $P=0.005$) were protective factors. Kaplan–Meier (KM) curves indicated that patients with NS-IgAN who did not receive ACEi/ARB had a worse renal prognosis than those who did (Fig. 2).

As shown in univariate analysis in Table 6, we found that a lower percentage of females (HR 0.47, $P=0.027$), higher MAP (HR 1.02, $P=0.006$), lower Hb (HR 0.98, $P=0.005$), higher UA (HR 1.01, $P<0.001$), lower eGFR (HR 0.096, $P<0.001$), the presence of Oxford classification S1 (HR 3.04, $P=0.013$), T1-2 (HR 7.0, $P<0.001$), C1-2 (HR 4.5, $P=0.039$) and failure to receive ACEi/ARB treatment (HR 0.038, $P=0.004$) were associated with a higher risk of ESKD progression or at least 50% eGFR decline among patients with IgAN-MsPGN. After adjusting for female, MAP, Hb, UA, S1 and T1-2, eGFR (HR 0.97, $P=0.031$), C1-2 (HR 6.06, $P=0.021$) and failure to receive ACEi/ARB treatment (HR 0.31, $P=0.005$) remained independent predictors for worse renal prognosis among patients with IgAN-MsPGN. Similarly, the results of the KM analysis suggested that compared to patients of MsGPN with ACEi/ARB treatment, those without had a worse renal prognosis (Fig. 3A).

Among patients with IgAN-MsPGN, 51 received OCT, and 27 received CPT (Table 7). Urinary protein levels in those receiving CPT were similar to those in the OCT group, but renal function was worse in the former than in the latter ($P=0.001$). There was no significant difference in RP and the development of renal endpoints between the OCT and CPT groups. Kaplan–Meier analysis showed that renal survivals were similar between groups ($P=0.500$) (Fig. 3B).

Patients with IgAN-MsPGN and Oxford classification C0 all received OCT. Among those with IgAN-MsPGN and C1, 28 received OCT, and 16 received CPT. Among those with IgAN-MsPGN and C2, 4 received OCT, and 10 received CPT. There was no significant difference in RP and the development of renal endpoints between patients with C1 or C2 treated with different corticosteroid regimens (Table 8).

Discussion

IgAN is the most prevalent primary glomerulonephritis worldwide, characterized by dominant IgA immunoglobulin deposition in kidney pathology. Clinical presentations include recurrent hematuria episodes, with or without proteinuria, hypertension, and renal insufficiency, leading to ESKD in a subset of patients. NS is an uncommon manifestation of IgAN, occurring in 5–15% of cases. A multicenter observational study in 2012 from South Korea reported that 100 out of 1076 IgAN patients (10.2%) presented with NS[4]. A retrospective study in 2017 from Japan found that 30(7.0%) out of 426 IgAN patients younger than 20 had NS. A 2019 study from China identified NS in 171 (14.7%) out of 1165 biopsy-proven IgAN patients (14.7%)[6], while another Chinese study reported 59 out of 1013 patients (5.8%) with biopsy-proven IgAN presenting with NS (5.8%)[7].

	ACEi/ARB - ($n=45$)	ACEi/ARB + ($n=88$)	eGFR ≥ 60 ($n=82$)	eGFR < 60 ($n=51$)
Male (%)	20 (44.4)	47 (53.4)	45 (54.9)	22 (43.1)
Age, years	29.67 ± 12.1	34.45 ± 14.12	30.41 ± 13.39†	36.73 ± 13.18
BMI, kg/m^2	22.92 ± 4.43	23.23 ± 3.13	22.85 ± 3.27	23.57 ± 4.08
Hypertension (%)	20 (44.4)	39 (44.3)	20 (24.4)†	39 (76.5)
Diabetes mellitus (%)	1 (2.2)	5 (5.7)	5 (6.1)	1 (2.0)
CVD (%)	1 (2.2)	–	–	1 (2.0)
SBP, mmHg	128.51 ± 23.28	131.58 ± 18.27	124.22 ± 18.62†	140.71 ± 18.2
DBP, mmHg	82.02 ± 17.32	82.6 ± 12.08	79.41 ± 12.16†	87.22 ± 15.5
MAP, mmHg	97.52 ± 18.22	98.93 ± 12.84	94.35 ± 13.29†	105.05 ± 14.9
Hb, g/L	129.27 ± 31.42	124.76 ± 22.68	136.33 ± 24.32†	110.14 ± 19.67
UA, μmol/L	456.91 ± 145.74	411.02 ± 100.89	395.9 ± 96.84†	475.82 ± 135.82
TC, mmol/L	8.65 ± 3.41*	7.43 ± 2.41	8.64 ± 3.06†	6.56 ± 1.83
TG, mmol/L	2.44 ± 1.58	2.28 ± 1.39	2.31 ± 1.5	2.38 ± 1.37
LDL-c, mmol/L	5.52 ± 2.7*	4.63 ± 1.71	5.49 ± 2.34†	4.05 ± 1.33
HDL-c, mmol/L	1.54 ± 0.64	1.44 ± 0.43	1.62 ± 0.55†	1.24 ± 0.34
Hematuria (%)	36 (80.0)	63 (71.6)	53 (64.6)†	46 ((90.2)
24-h proteinuria, g/d	6.66 ± 3.51	6.38 ± 3.66	6.37 ± 3.62	6.64 ± 3.6
ALB, g/L	23.47 ± 5.58	24.49 ± 4.84	22.86 ± 5.37†	26.22 ± 3.89
Serum C3, g/L	1.06 ± 0.36	1.02 ± 0.18	1.06 ± 0.17	0.99 ± 0.35
Scr, μmol/L	161.27 ± 118.04*	114.57 ± 59.79	79.48 ± 22.5†1	212.2 ± 88.78
eGFR (ml/min/1.73m^2)	70.78 ± 44.05	79.83 ± 39.68	103.3 ± 28.22†	34.12 ± 14.03
M1 (%)	41 (91.1)	77 (87.5)	68 (82.9)†	50 (98.0)
E1 (%)	10 (22.2)	28 (31.8)	22 (26.8)	16 (31.4)
S1 (%)	16 (35.6)	39 (44.3)	19 (23.2)†	36 (70.6)
T1-2 (%)	20 (44.4)	33 (37.5)	12 (14.6)†	41 (80.4)
C1-2 (%)	22 (48.9)	53 (60.2)	32 (39.0)†	43 (84.3)
C3 deposition (%)	29 (64.4)	56 (63.6)	42 (51.2)†	43 (84.3)
C1q deposition (%)	8 (17.8)	9 (10.2)	8 (9.8)	9 (17.6)
Glomerulosclerosis proportion	0.26 ± 0.3	0.19 ± 0.2	0.09 ± 0.15†	0.41 ± 0.22

Table 3. Clinicopathological manifestations of patients with NS-IgAN and comparisons between different subtypes. *ACEi/ARB* - without angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers therapy, *ACEi/ARB* + with ACEi/ARB therapy, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *Hb* hemoglobin, *UA* uric acid, *TC* total cholesterol, *TG* triglyceride (TG), *HDL-c* high-density lipoprotein, *LDL-c* low-density lipoprotein cholesterol, *ALB* serum albumin, *C3* complement factor 3, *Scr* serum creatinine, *eGFR* estimated glomerular filtration rate, *M* mesangial hypercellularity, *E* endocapillary proliferation, *S* segmental sclerosis or adhesion, *T* tubular atrophy/interstitial fibrosis, *C* crescents, *C3* complement factor 3, *C1q* complement factor 1q. *Comparison between patients with ACEi/ARB - and ACEi/ARB +, $P<0.05$. †Comparison between patients with eGFR ≥ 60 and eGFR < 60, $P<0.05$.

Our study found that 5.6% of patients with biopsy-proven IgAN presented with NS, aligning with previous research findings.

Existing reports focusing on patients with NS-IgAN are primarily aimed at comparing differences in clinical features and renal prognosis between those with IgAN presenting with and without NS. It is expected that those with NS-IgAN had worse renal function, more severe pathological lesions, and poorer long-term outcomes than those without NS[4,6,7], except patients with renal pathology resembling MCD. However, following the publication of the 2021 KDIGO guideline on glomerulonephritis[8], the significance of further dividing pathological subtypes in patients with NS-IgAN becomes clear. Our cohort is the first to analyze differences in clinical presentations, pathological features, therapeutic response, and renal outcomes between patients with NS-IgAN and various renal biopsy findings.

IgAN belongs to mesangial proliferative glomerulonephritis, characterized by the predominance of IgA immune complexes depositions in the mesangial area. According to the 2021 KDIGO guideline, patients with NS-IgAN and pathological features of IgAN-MsPGN should receive the same treatment as those with a high risk of progressive CKD despite maximal supportive care[8]. In this study, most patients with NS-IgAN had pathological manifestations of IgAN-MsPGN. Among them, 51 (59.3%) received OCT initially, while 27 (31.4%) received CPT for managing crescentic lesions. When comparing clinical features between those receiving OCT and CPT, we found that the eGFR levels of patients receiving CPT were worse than those of patients receiving OCT, but their renal prognosis did not differ.

	ACEi/ARB − ($n=45$)	ACEi/ARB + ($n=88$)	eGFR ≥ 60 ($n=82$)	eGFR < 60 ($n=51$)
ACEi/ARB (%)	–	88 (100.0)	56 (68.3)	32 (62.7)
SGLT-2i (%)	–	–	–	–
OCT (%)	32 (74.4)	62 (70.5)	70 (85.4)†	24 (49.0)
CPT (%)	6 (14.0)*	23 (26.1)	10 (12.2)†	19 (38.8)
Modified POZZI therapy (%)	–	2 (2.3)	1 (1.2)†	1 (2.0)
Immunosuppressant (%)	3 (6.7)*	23 (26.1)	16 (19.5)	10 (19.6)
Follow-up time (months)	38.4 ± 39.58*	59.06 ± 44.77	60.3 ± 44.6†	38.82 ± 40.09
Hematuria (%)	11 (55.0)	34 (54.0)	19 (42.2)†	26 (68.4)
Proteinuria remission (%)	18 (58.1)	49 (72.1)	50 (87.7)†	17 (40.5)
Renal endpoint event (%)	18 (40.0)*	19 (21.6)	7 (8.5)†	30 (58.8)

Table 4. Treatment and prognosis of patients with NS-IgAN and comparisons between different subtypes. *ACEi/ARB* - without angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers therapy, *ACEi/ARB* + with ACEi/ARB therapy, *SGLT-2i* sodium-dependent glucose transporters 2 inhibitors, *OCT* oral corticosteroid therapy, *CPT* corticosteroid pulse therapy. *Comparison between patients with ACEi/ARB - and ACEi/ARB +, $P<0.05$. †Comparison between patients with eGFR ≥ 60 and eGFR < 60, $P<0.05$.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
MAP, mmHg	1.04 (1.02–1.05)	< 0.001*	1.02 (0.99–1.04)	0.167
Hb	0.96 (0.95–0.98)	< 0.001*	0.99 (0.98–1.01)	0.451
UA	1.01 (1–1.01)	< 0.001*	1.002 (1–1.01)	0.078
ALB	1.16 (1.07–1.26)	0.001*	0.99 (0.88–1.12)	0.866
eGFR	0.95 (0.94–0.97)	< 0.001*	0.98 (0.96–0.99)	0.010*
S1	7.99 (3.32–19.21)	< 0.001*	1.83 (0.63–5.29)	0.267
T1-2	15.98 (5.65–45.2)	< 0.001*	3.39 (1.05–10.94)	0.042*
C1-2	15.47 (3.71–64.41)	< 0.001*	5.71 (1.24–26.22)	0.025*
C3 deposition	4.65 (1.65–13.12)	0.004*	1.07 (0.36–3.16)	0.904
ACEi/ARB	0.39 (0.2–0.75)	0.004*	0.31 (0.14–0.7)	0.005*

Table 5. COX regression analysis of factors associated with poor renal outcome among patients with NS-IgAN. *HR* hazard ratio, *CI* confidence interval, *MAP* mean arterial pressure, *Hb* hemoglobin, *UA* uric acid, *ALB* serum albumin, *eGFR* estimated glomerular filtration rate, *S* segmental sclerosis or adhesion, *T* tubular atrophy/interstitial fibrosis, *C* crescents, *C3* complement factor 3, *ACEis* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers. *$P<0.05$.

A subset of patients with NS-IgAN exhibit MCD-like pathological features, presenting clinical manifestations, responses to steroid therapy, and prognoses similar to those observed in MCD patients. This group is referred to as having minimal change IgAN[18]. This subgroup was first identified in 1983 by Mustonen et al.., who described three cases of NS-IgAN showing pathological changes reminiscent of MCD alongside mesangial IgA[19] deposits. Following this initial report, similar cases have been successively identified, especially among Asian populations. A prospective cohort study from China included 27 patients with IgAN-MCD, all of whom achieved CR within eight weeks of corticosteroid treatment[20]. This finding suggests that corticosteroids are indeed effective for managing patients with IgAN-MCD. Another retrospective multicenter cohort from Korea studied 46 patients with IgAN-MCD and matched them with 138 patients with MCD as controls. They showed no difference in the rate of proteinuria remission and renal prognosis between patients with IgAN-MCD and MCD only[21]. In our cohort, 23.67% of patients with NS-IgAN had MCD-like pathological changes. After a follow-up of 63.68 ± 52.38 months, all 37 patients with IgAN-MCD received OCT, and 95.8% achieved proteinuria remission without developing renal endpoints. The 2021 KDIGO guideline opined that it is currently unclear whether these patients can be categorized as a specific IgAN variant or whether the presence of MCD should be reassured in a patient with IgAN[8]. A study from China using paraffin-embedded kidney tissues from 24 patients with IgAN-MCD and 24 matched patients with IgAN to perform double immunofluorescent (IF) staining of IgA and galactose-deficient IgA1 (Gd-IgA1). They demonstrated that Gd-IgA1 depositions were mainly distributed in the mesangial area with IgA co-deposits in the kidney tissues of those with IgAN-MCD, similar to findings in patients with IgAN[10]. They concluded that IgAN-MCD represented a dual glomerulopathy, mild IgAN with superimposed MCD. However, due to the low incidence of IgAN-MCD cases, more large-scale research is needed to explore the pathogenesis of IgAN-MCD.

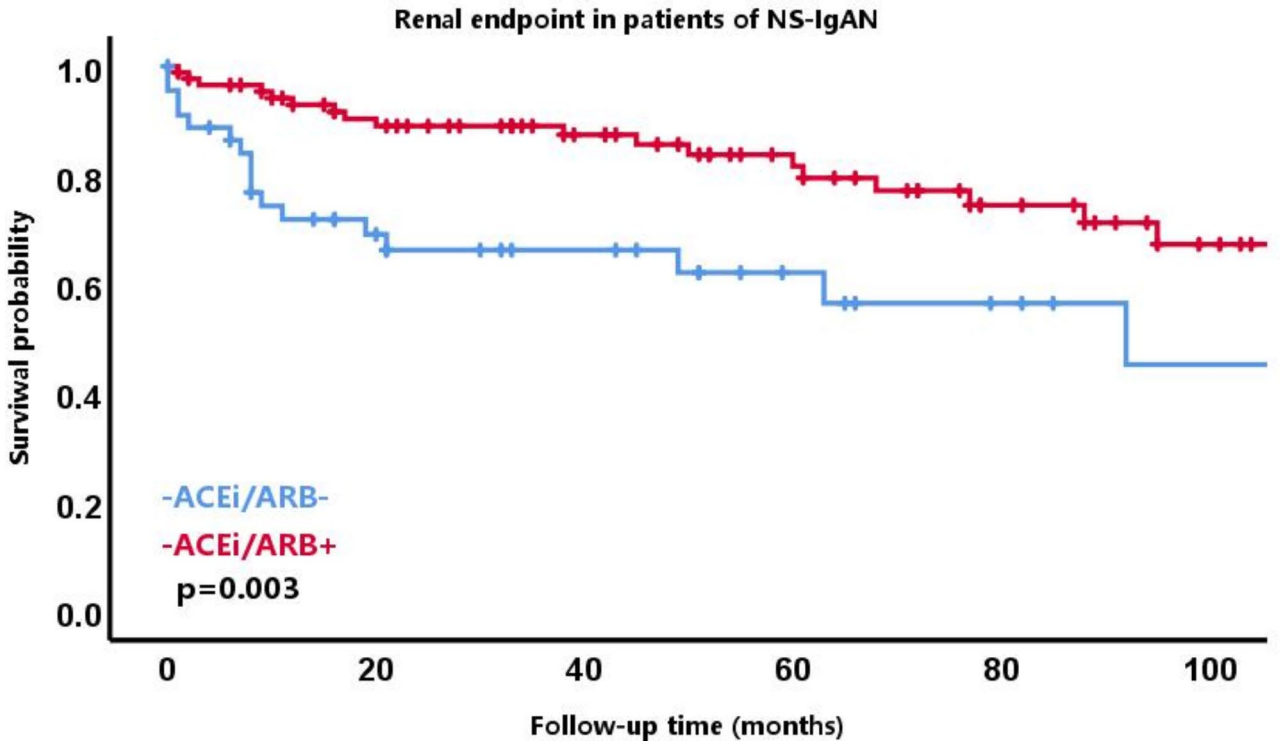

Fig. 2. The probability of renal survival among patients of NS-IgAN with and without ACEi/ARB therapy. *NS-IgAN* immunoglobulin (Ig)A nephropathy with nephrotic syndrome, *ACEi/ARB* - without angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers therapy, *ACEi/ARB* + with ACEi/ARB therapy.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Female	0.47 (0.24–0.92)	0.027*	0.54 (0.23–1.26)	0.155
MAP	1.02 (1.01–1.04)	0.006*	1.02 (1–1.04)	0.129
Hb	0.98 (0.96–0.99)	0.005*	0.99 (0.98–1.01)	0.393
UA	1.01 (1–1.01)	< 0.001*	1 (0.098–1.001)	0.430
eGFR	0.96 (0.94–0.98)	< 0.001*	0.98 (0.96–1)	0.025*
S1	3.04 (1.26–7.34)	0.013*	1.43 (0.51–4.01)	0.503
T1-2	7.0 (2.47–19.79)	< 0.001*	2.83 (0.9–8.92)	0.075
C1-2	4.5 (1.08–18.76)	0.039*	6.06 (1.31–28.03)	0.021*
ACEi/ARB	0.38 (0.2–0.74)	0.004*	0.31 (0.14–0.7)	0.005*

Table 6. COX regression analysis of factors associated with poor renal outcome among patients with IgAN-MsPGN. *MAP* mean arterial pressure, *Hb* hemoglobin, *UA* uric acid, *eGFR* estimated glomerular filtration rate, *S* segmental sclerosis or adhesion, *T* tubular atrophy/interstitial fibrosis, *C* crescents, *ACEis* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers. *$P < 0.05$.

IgAN and MN are common categories of glomerulonephritis, and the co-existence of both categories in the same patient (IgAN-MN) has been described anecdotally. In 2022, a prospective study from China identified 137, 100, and 100 patients with IgAN-MN, IgAN only, and MN only, respectively, and compared the clinical-pathological characteristics, serum Gd IgA1, anti-phospholipase A2 receptor antibody (anti-PLA2R) levels, and disease-specific genetic risk scores between the three groups. They showed that, compared to those with IgAN, patients with IgAN-MN might exhibit more similar features to those with MN[22]. Another study revealed that the clinical and pathological characteristics of patients with IgAN-MN were similar to those of patients with MN. The former had a high proteinuria CR rate (80%) after steroid-combined immunosuppressive therapy[23]. However, few studies reported the long-term prognosis of these patients. In this study, among patients with NS-IgAN, 7 had IgAN-MN, and 5 received follow-up for an average of 72.29 ± 27.92 months. All five patients with IgAN-MN had RP during follow-up, and none developed the renal endpoint.

This study has several limitations. Firstly, it is a single-center, retrospective analysis with a relatively small sample size. Secondly, the patient cohort was identified over two decades, introducing a high dropout rate and

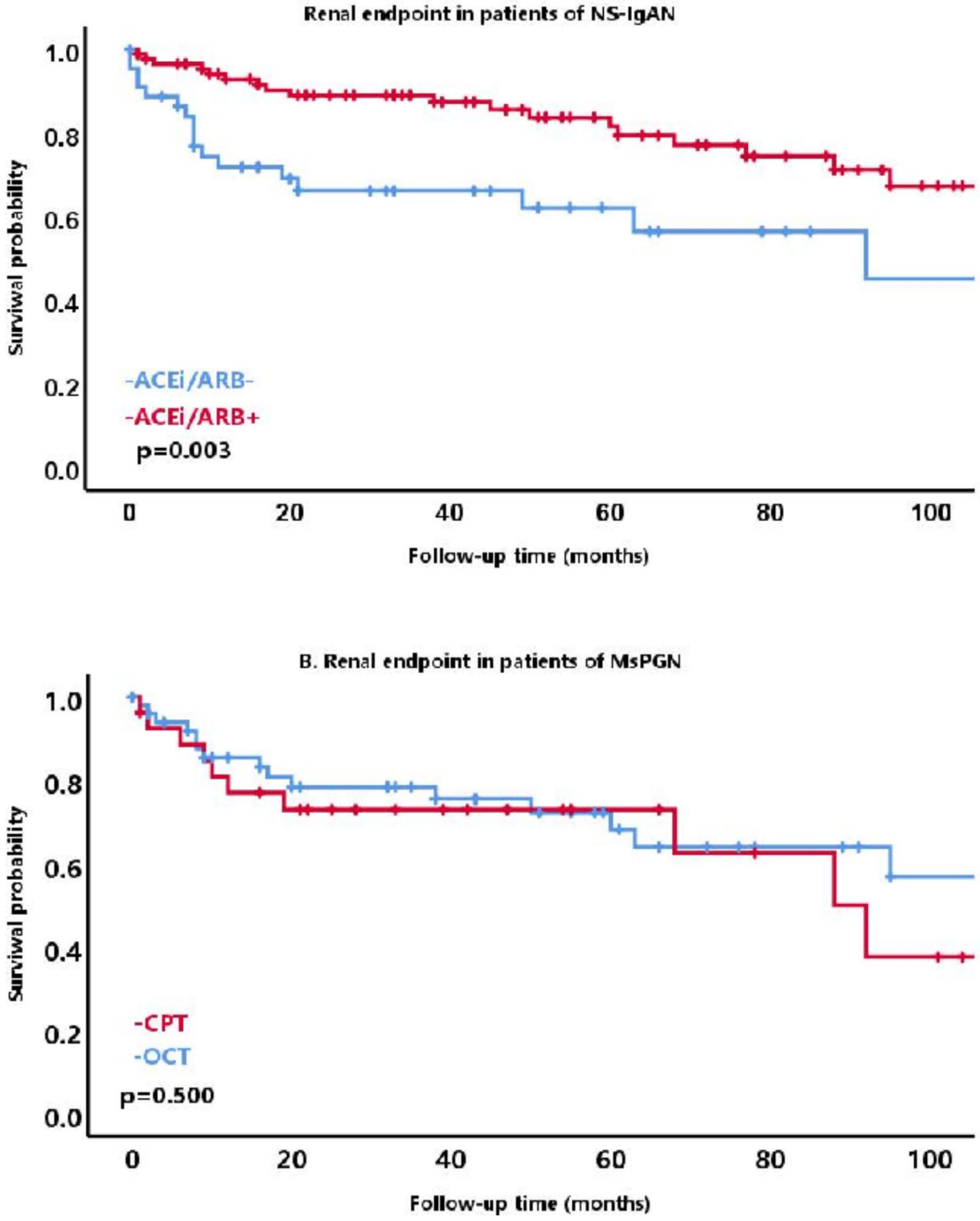

Fig. 3. The probability of renal survival among patients of IgAN-MsPGN. *IgAN-MsPGN* IgAN with mesangial proliferative glomerulonephritis, *ACEi/ARB* - without angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers therapy, *ACEi/ARB* + with ACEi/ARB therapy, *OCT* oral corticosteroid therapy, *CPT* corticosteroid pulse therapy.

potential selection bias in the final analysis. Consequently, a study with a larger sample size and a multicenter prospective cohort design is warranted to more comprehensively investigate the treatment efficacy of various therapeutic approaches and identify significant factors impacting the long-term renal prognosis among patients with NS-IgAN across different pathological types.

	OCT ($n=51$)	CPT ($n=27$)	P
24-h proteinuria (g/day)	5.54 ± 2.9	6.75 ± 4.15	0.138
eGFR (ml/min/1.73m^2)	73.4 ± 40.88	50 ± 21.56	0.001*
Proteinuria remission (%)	25 (64.1)	10 (41.7)	0.084
Renal endpoint event (%)	17 (33.3)	10 (37.0)	0.745

Table 7. Prognostic differences according to steroid treatment regimens among patients with IgAN-MsPGN. *OCT* oral corticosteroid therapy, *CPT* corticosteroid pulse therapy, *eGFR* estimated glomerular filtration rate. *$P<0.05$.

	C1			C2		
Treatment	OCT ($n=28$)	CPT ($n=16$)	P	OCT ($n=4$)	CPT ($n=10$)	P
24-h proteinuria (g/day)	5.02 ± 2.13	5.71 ± 2.34	0.319	5.05 ± 1.29	8.26 ± 5.7	0.200
eGFR (ml/min/1.73m^2)	65.32 ± 35.21	50.82 ± 23.02	0.148	58.34 ± 43.04	48.81 ± 20.26	0.626
Proteinuria remission (%)	13 (59.1)	5 (35.7)	0.178	2 (20.0)	5 (50.0)	0.724
Renal endpoint event (%)	11 (39.3)	7 (43.8)	0.775	4 (66.7)	3 (27.3)	0.126

Table 8. Prognostic differences among patients with IgAN-MsPGN and different crescentic lesion severities receiving various steroid treatment regimens. *OCT* oral corticosteroid therapy, *CPT* corticosteroid pulse therapy, *eGFR* estimated glomerular filtration rate.

Conclusions

In conclusion, our study has successfully demonstrated that patients with NS-IgAN can be classified into four distinct pathological phenotypes. The findings strongly support the presence of significant differences in clinical-pathological characteristics, efficacy of steroid treatment, and long-term prognosis among patients with NS-IgAN across different pathological types. Consequently, further delineation of the pathological features within the NS-IgAN patient population holds substantial value for guiding therapeutic decisions and enhancing prognostic outcomes.

Data availability

The authors declare that all data supporting the findings of this study are available within the paper. The results presented in this paper have not been published previously in whole or part.

Received: 17 September 2024; Accepted: 8 January 2025
Published online: 13 January 2025

References

1. McGrogan, A., Franssen, C. F. & de Vries, C. S. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. *Nephrol. Dial Transpl.* **26**, 414–430 (2011).
2. Barbour, S. J. et al. The MEST score provides earlier risk prediction in lgA nephropathy. *Kidney Int.* **89**, 167–175 (2016).
3. Pitcher, D. et al. Long-term outcomes in IgA Nephropathy. *Clin. J. Am. Soc. Nephrol.* **18**, 727–738 (2023).
4. Kim, J. K. et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. *Clin. J. Am. Soc. Nephrol.* **7**, 427–436 (2012).
5. Shima, Y. et al. IgA nephropathy with presentation of nephrotic syndrome at onset in children. *Pediatr. Nephrol.* **32**, 457–465 (2017).
6. Han, X. et al. Clinical and pathological features of immunoglobulin A nephropathy patients with nephrotic syndrome. *Clin. Exp. Med.* **19**, 479–486 (2019).
7. Li, H. et al. The difference between patients with nephrotic syndrome and nephrotic-range proteinuria in IgA nephropathy: a propensity score matched cohort study. *BMC Nephrol.* **23**, 163 (2022).
8. Kidney Disease. Improving global outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the management of glomerular diseases. *Kidney Int.* **100**, S1–s276 (2021).
9. Cattran, D. C. et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int.* **76**, 534–545 (2009).
10. Li, H. et al. Immune characteristics of IgA Nephropathy with Minimal Change Disease. *Front. Pharmacol.* **12**, 793511 (2021).
11. Chen, P. et al. Characteristics of patients with coexisting IgA nephropathy and membranous nephropathy. *Ren. Fail.* **40**, 213–218 (2018).
12. Andeen, N. K. et al. IgA-dominant glomerulonephritis with a membranoproliferative pattern of injury. *Hum. Pathol.* **81**, 272–280 (2018).
13. Schena, F. P., Gesualdo, L. & Montinaro, V. Immunopathological aspects of immunoglobulin A nephropathy and other mesangial proliferative glomerulonephritides. *J. Am. Soc. Nephrol.* **2**, S167–172 (1992).
14. Wang, Y. et al. Comparative analysis between the safety and efficacy of oral corticosteroids versus corticosteroids pulse therapies in IgA nephropathy. *Ren. Fail.* **45**, 2255683 (2023).
15. Ochi, A., Moriyama, T., Takei, T., Uchida, K. & Nitta, K. Comparison between steroid pulse therapy alone and in combination with tonsillectomy for IgA nephropathy. *Int. Urol. Nephrol.* **45**, 469–476 (2013).
16. Lv, J. et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA* **318**, 432–442 (2017).

17. Medjeral-Thomas, N. R., Cook, H. T. & Pickering, M. C. Complement activation in IgA nephropathy. *Semin Immunopathol.* **43**, 679–690 (2021).
18. Li, X. W. et al. Comparison between patients with IgA nephropathy with minimal change disease and patients with minimal change disease. *Clin. Nephrol.* **85**, 273–281 (2016).
19. Mustonen, J., Pasternack, A. & Rantala, I. The nephrotic syndrome in IgA glomerulonephritis: response to corticosteroid therapy. *Clin. Nephrol.* **20**, 172–176 (1983).
20. Wang, J., Juan, C., Huang, Q., Zeng, C. & Liu, Z. Corticosteroid therapy in IgA nephropathy with minimal change-like lesions: a single-centre cohort study. *Nephrol. Dial Transpl.* **28**, 2339–2345 (2013).
21. Cho, W. H. et al. Characterization of IgA Deposition in the kidney of patients with IgA nephropathy and minimal change. *J. Clin. Med.* **9**, (2020).
22. He, J. W. et al. Concurrent IgA nephropathy and Membranous Nephropathy, is it an overlap. *Syndrome? Front. Immunol.* **13**, 846323 (2022).
23. Saleem, N. et al. Analysis of clinical, pathological and prognostic features of Coexistent Membranous and IgA Nephropathy in a series of 13 patients at a Tertiary Care. *Hosp. Cureus*. **13**, e18006 (2021).

Author contributions
QW, WC and LHJ conceived the study, YQW and LT participated in its design and conduction. LHJ, YQW and LT collected clinical data. LHJ and QW analyzed and interpreted data. LHJ and QW contributed to the writing of the manuscript. All authors read and approved the final manuscript for submission.

Funding
This work was supported by grants from the National Natural Science Foundation of China (Nos. 81970599, 82170737, 82370707), the National Key Research and Development Project of China (No. 2021YFC2501302), Key Laboratory of National Health Commission, Key Laboratory of Nephrology, Guangdong Province, Guangzhou, China (Nos. 2002B60118 and 2020B1212060028) and Guangdong International Science and Technology Cooperation Institute of Immune Kidney Disease and Precision Medicine.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and informed consent statement
All experiments on human subjects were conducted per the Declaration of Helsinki. This study was approved by the ethical committee for clinical research and animals of the First Affiliated Hospital of Sun Yat-sen University, and informed consent was obtained from all subjects.

Additional information
Correspondence and requests for materials should be addressed to Q.W.