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Prognostic factors affecting long-term outcomes in patients with concurrent IgA nephropathy and membranous nephropathy

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ABSTRACT

Background: The incidence of concurrent immunoglobulin A nephropathy and membranous nephropathy (cIgAN/MN) is low and rarely reported, and the prognosis of patients with cIgAN/MN remains unclear. This study was designed to compare the clinical and prognostic characteristics of cIgAN/MN with IgAN and MN and to identify crucial factors influencing the outcomes of patients with cIgAN/MN.

Methods: We included biopsy-proven cIgAN/MN patients between December 2012 and December 2020 at Xijing Hospital. In the same period, propensity score matching was employed to select an equal number of IgAN and MN patients according to the following criteria: age, sex, and follow-up time. The primary endpoint was defined as a composite of eGFR decline ≥30 %, end-stage renal disease, or death. The patient survival rate was examined using Kaplan–Meier survival curves. Univariate and multivariate Cox regression analysis models were utilized to identify the risk factors affecting renal prognosis.

Results: A total of 135 patients were finally included in this study and 35 (25.9 %) reached the primary endpoint. The median follow-up time of cIgAN/MN was 45.9 (24.0, 72.0) months. Compared to the IgAN group, the cIgAN/MN group exhibited a lower cumulative incidence rate of composite renal endpoints ($P = 0.044$), while no significant difference was found between MN and cIgAN/MN patients ($P = 0.211$). Univariate Cox analysis revealed that mean arterial pressure, serum potassium, blood urea nitrogen, serum IgA, segmental glomerulosclerosis (S1), and MN staging were associated with an increased risk of renal composite endpoints. The multivariate Cox regression analysis of clinical variables plus histological lesion scoring demonstrated that potassium (HR = 14.350, 95 % CI 2.637–78.090, $P = 0.002$), serum IgA (HR = 1.870, 95 % CI 1.109–3.153, $P = 0.019$), and S1 (HR = 11.965, 95 % CI 2.166–66.105, $P = 0.004$) were independent risk factors influencing renal outcomes in cIgAN/MN patients.

Conclusion: The prognosis of cIgAN/MN patients may exhibit an intermediate pattern between IgAN and MN, leaning towards being more similar to MN in certain aspects. Within the cIgAN/

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MN cohort, potassium, and serum IgA may be more predictive of rapid progression of renal endpoints, and S1 may indicate a more aggressive disease course.

1. Introduction

Immunoglobulin A nephropathy (IgAN) and membranous nephropathy (MN) are the predominant types of glomerulonephritis in the Asian-Pacific region and even worldwide [1]. Both diseases are immune complex-mediated glomerular diseases, but their pathogenesis is different. IgAN is characterized by the deposition of IgA immune complexes in the glomeruli, leading to inflammation and damage. Approximately 30–40 % of IgAN patients progress to end-stage renal disease (ESRD) within a 20-year timeframe [2]. On the other hand, MN is caused by the formation of immune complexes against intrinsic glomerular antigens, characterized by staining of IgG, IgG4, phospholipase-A2-receptor (PLA2R), or other novel multiple immune complexes (FCN3, CD206, EEA1, etc.) [3] in glomerular capillaries, resulting in thickening of the glomerular basement membrane (GBM) and impaired kidney function [4]. The pathogenesis of both diseases is uncertain. It is crucial to differentiate between these two conditions to provide appropriate treatment and management strategies for patients in clinical practice and research. However, once the two pathological types appear in the same patient, clinicians face challenges.

The coexistence of both mesangial IgA and subepithelial IgG deposits in the glomeruli in primary glomerular disease was first reported in 1983 [5]. Subsequently, in several studies, scholars have described the pathological features and clinical characteristics of patients with concurrent IgAN and MN (cIgAN/MN) [6–10]. cIgAN/MN predominantly manifests with proteinuria and microscopic haematuria, with positive serum anti-PLA2R detected in approximately 50–70 % of patients [9]. Histologically, cIgAN/MN is characterized by two components, with milder IgA deposition in mesangial areas compared to IgAN patients and weaker IgG and C3 deposition along the glomerular basement membrane than in MN patients [8]. In fact, the incidence of cIgAN/MN in renal biopsy cases is relatively low, with patients accounting for only 0.05–0.1 % [11,12]. Previous studies on cIgAN/MN have mainly focused on the description of renal pathology and case reports, and they have shown that the combination of these two pathological processes does not seem to result in a more severe clinical presentation for patients [7,8]. However, there is still a lack of systematic exploration of the prognosis and risk factors of the disease as well as long-term clinical studies on the prognosis of patients with cIgAN/MN [10]. The question of whether cIgAN/MN is only a concurrent or overlap syndrome is still inconclusive.

Therefore, in this study, we aim to fill this gap by comparing long-term (8-year) outcomes in IgAN, MN, and cIgAN/MN patients, and to explore the risk factors for the long-term prognosis of cIgAN/MN patients, thereby providing evidence-based medical guidelines for clinical decision-makers.

2. Materials and methods

2.1. Study objective

We conducted a retrospective review of the pathological and clinical data of patients diagnosed with cIgAN/MN through renal biopsy at Xijing Hospital (Air Force Medical University) from December 2012 to December 2020. Patients who underwent percutaneous renal biopsy with ultrasound guidance and had reports of light microscopy, electron microscopy and immunofluorescence examinations were included. Exclusion criteria were as follows: (1) absence of original pathological reports; (2) fewer than 8 glomeruli observed in the biopsy specimens; (3) secondary nephropathy, including lupus nephritis, hepatitis B associated glomerulonephritis, and Sjogren's syndrome; and (4) presence of other major diseases with an expected survival period of less than 1 year. The established primary glomerular disease database of Xijing Hospital [13] was used to search the same number of IgAN and MN patients in the same period for matching. Propensity score matching (PSM) and nearest neighbour matching (1:1) control groups were used, with calliper widths of 0.1 standard deviation in the control group without replacement. The control variables selected in the PSM were age, sex, and follow-up time. This study was approved by the Ethics Committee of Xijing Hospital and conducted following the Helsinki Declaration (ethical number: KY20213027-1). Due to the retrospective design, the Ethics Committee waived the requirement for informed consent from eligible patients.

2.2. Data collection

Two researchers (Qin and Zhao) collected baseline data on patients' renal biopsies from the electronic medical record information system, including demographic, clinical, and pathological characteristics. Variables with missing data exceeding 10 % and variables with a correlation coefficient greater than 0.75 were excluded. Multiple imputation was used to impute missing data. The treatment methods of included patients in this study were classified into the following 4 types: supportive therapy, corticosteroids alone, immunosuppressants alone, and corticosteroids plus immunosuppressants. Among the group of immunosuppressive agents, we evaluated the effect of the utilization of cyclophosphamide on prognosis separately. Pathological characteristics were reviewed by experienced pathologists and classified using the Oxford Classification (MEST-C score, including mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy, and crescents) [14] of IgAN and cIgAN/MN. MN was classified into four stages (I, II, III, and IV) according to the location of the subepithelial deposits and matrix accumulation [15]. The intensity of the immunofluorescence staining was graded using a semiquantitative scale (range: 0 to 4), and a grade of 1 higher was

considered positive.

Patients with a follow-up duration exceeding 6 months were considered successful cases. Detailed follow-up data was to be recorded, including general clinical symptom, medication history, renal function, and urine analysis. Follow-up included assessment of survival status, progression to ESRD or dialysis, and laboratory examination data. We strictly protected the privacy of the subjects' information during and after data collection.

2.3. Definition

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16]. ESRD is defined as eGFR less than 15 ml/min/1.73 m^2, requiring initiation of chronic dialysis (hemodialysis or peritoneal dialysis) or kidney transplantation. Follow-up refers to the time interval between renal biopsy and the last outpatient visit or last telephone record. Complete remission (CR) of urinary protein is defined as urine protein $<$0.3 g/24h, confirmed by at least two values with a one-month interval, accompanied by normal serum creatinine level and normal serum albumin concentration. Partial remission (PR) of urinary protein is defined as a decrease in urine protein of at least 50 % from the peak value and $<$3.5 g/24h, accompanied by stable serum creatinine and improvement or normalization of serum albumin concentration [17]. The primary endpoint used in this study was the composite endpoint of eGFR decline $\geq$30 %, ESRD, or death. The secondary endpoint was the composite endpoint of urinary protein CR and PR.

2.4. Statistical analysis

Categorical variables were described using frequencies and percentages, and comparisons were performed using the $\chi 2$ test or Fisher's exact test. Normally distributed continuous variables were presented as the mean $\pm$ standard deviation (SD), while non-normally distributed continuous variables were expressed as the median (interquartile ranges). Comparisons between groups were conducted using Student's *t*-test or the Mann-Whitney *U* test. Kaplan-Meier curves were used to describe the cumulative survival of the patients and were compared between groups with the use of the log-rank test. Univariate and multivariate Cox regression analyses were conducted to explore the risk factors influencing renal prognosis in cIgAN/MN patients. In multivariable Cox regression analyses, we used a forward stepwise selection algorithm to identify independent predictors and build two adjusted models, including baseline clinical variables and further plus histological lesion scoring. Before conducting the multivariate Cox regression analysis, we tested the proportional risk assumption to ensure the accuracy of the model. To assess the time-dependent effect of variables, we compared the effect of variables with the follow-up time. If the proportional risk assumption was found to be violated, we fitted the model accordingly. The maximally selected rank statistics method (MSRSM) was used to determine the optimal cutoff values for continuous variables corresponding to the most significant association with survival outcomes by the Jsurvival - Survival Module of ClinicoPath in Jamovi software. *P* values were calculated using two-tailed tests, and a significance level of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (Version26.0, IBM) and Jamovi (Version 2.3, Sydney, Australia).

3. Results

3.1. Patient characteristics

In this study, a total of 45 eligible cIgAN/MN patients were included from 52 identified patients among 3682 renal biopsy patients. Additionally, 45 matched controls were identified from 993 primary IgAN patients and 809 primary MN patients. Finally, 135 patients from the three groups were included in the analysis (Fig. 1). We collected 73 variables from the electronic medical records and a total

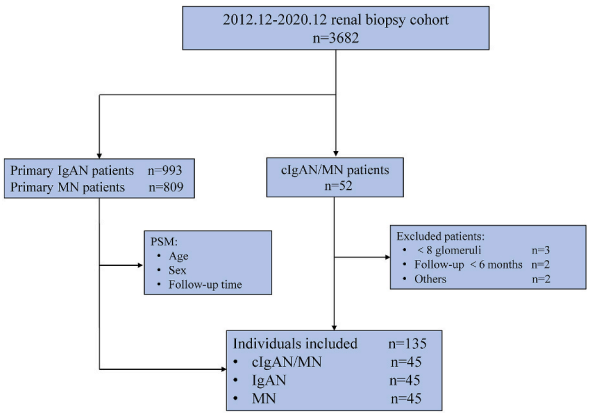

Fig. 1. Inclusion flowchart. IgAN, immunoglobulin A nephropathy. MN, membranous nephropathy. cIgAN/MN, concurrent IgAN and MN. PSM, propensity score matching.

of 57 covariates were included after rigorous screening, including demographic characteristics, clinical manifestations, pathological features, and treatment strategies (Table S1). The baseline data on renal biopsies from enrolled patients are presented in Table 1. Compared to IgAN patients, cIgAN/MN patients exhibited significantly higher levels of 24h urine total protein (UTP) and lower albumin (ALB), serum creatinine and blood urea nitrogen (BUN) levels. No significant differences in other baseline parameters were found between the cIgAN/MN and MN groups. At the initial treatment after renal biopsy, the treatment of cIgAN/MN is mainly supportive therapy and corticosteroids plus cyclophosphamide.

3.2. Pathological features

Renal biopsy revealed thickening of the GBM in cIgAN/MN patients, and along with the persistence of deposits, the GBM matrix reaction revealed small spike-like protrusions visualized by silver stain (Fig. 2A and B). Immunofluorescence staining showed that IgA (Fig. 2C), IgG (Fig. 2D) and C3 (Fig. 2E) were predominant in the glomerular capillary wall. The presence of subepithelial electron dense material was observed under electron microscope (Fig. 2F). The pathological features of all patients in the renal biopsy results are presented in Table 2. Under light microscopy, compared with cIgAN/MN patients, the glomerular sclerosis rate was higher in IgAN patients ($P < 0.001$), but similar to that in MN group ($P = 0.416$). The segmental sclerosis rate was lower in cIgAN/MN patients based on the Oxford classification ($P < 0.001$). By immunofluorescence, IgA deposition was similar ($P = 0.350$), but IgG ($P < 0.001$), IgM ($P < 0.001$) and C3 ($P = 0.007$) were significantly heavier in cIgAN/MN patients than in IgAN patients. Compared with MN patients, IgG deposition was weaker ($P < 0.001$) and IgM($P < 0.001$) and C3 ($P = 0.023$) deposition was relatively heavier in cIgAN/MN patients. Under electron microscopy, the staging of cIgAN/MN patients was significantly different from that of MN patients ($P = 0.005$), with stage II predominating in MN (57.8 %) and stage I predominating in cIgAN/MN (64.4 %).

Table 1
Baseline and follow-up characteristics of the study subjects.

Characteristics	cIgAN/MN (n = 45)	IgAN (n = 45)	MN (n = 45)	P (cIgAN/MN vs IgAN)	P (cIgAN/MN vs MN)
Baseline (at renal biopsy)					
Age, years	42.7 ± 14.5	42.4 ± 16.8	46.9 ± 15.2	0.241	0.245
Male, n (%)	26 (57.8)	28 (62.2)	28 (62.2)	0.667	0.667
Married, n (%)	37 (82.2)	35 (77.8)	40 (88.9)	0.598	0.368
Body mass index, kg/m^2	23.2 ± 3.6	24.2 ± 4.5	26.0 ± 3.7	0.310	0.763
MAP, mmHg	91.9 ± 11.8	96.5 ± 15.12	98.3 ± 12.6	0.041	0.414
UTP, mg/24h	2680 (1200, 4840)	950.0 (700, 1562)	2522.0 (1600, 5525)	< 0.001	0.453
>3.5 g/24h, n (%)	15 (33.3)	3 (6.7)	19 (42.2)	< 0.001	0.384
WBC, 10^9/L	6.86 ± 2.10	6.92 ± 2.01	7.82 ± 2.58	0.878	0.269
Hb, g/L	136.5 ± 20.0	135.8 ± 22.0	138.7 ± 21.3	0.881	0.898
TP, g/L	53.1 ± 12.2	65.8 ± 7.4	52.4 ± 9.7	< 0.001	0.060
Globulin, g/L	23.4 ± 5.5	26.8 ± 4.7	25.8 ± 4.9	0.002	0.431
Alb, g/L	29.9 ± 8.5	39.0 ± 6.5	26.6 ± 8.2	0.002	0.683
TC, mmol/L	6.07 (4.43, 7.54)	4.52 (3.75, 5.34)	6.67 (5.48,8.52)	< 0.001	0.150
TG, mmol/L	1.81 (1.22, 2.78)	1.41 (1.04, 1.86)	2.61 (2.01, 3.91)	0.039	0.002
HDL-C, mmol/L	1.36 (1.19, 1.81)	1.24 (1.00, 1.49)	1.41 (1.77,1.23)	0.026	0.637
LDL-C, mmol/L	4.16 (2.54, 5.00)	2.65 (2.21, 3.40)	3.94 (5.45,3.25)	0.002	0.504
Serum creatinine, μmol/L	83.6 ± 26.3	100.0 ± 42.8	87.8 ± 28.4	0.131	0.959
eGFR, mL/min/per 1.73m^2	91.3 ± 25.4	81.0 ± 29.8	86.3 ± 24.9	0.371	0.828
BUN, mmol/L	5.0 ± 1.8	6.5 ± 3.7	5.4 ± 2.4	0.153	0.144
CysC, mg/L	0.85 (0.77, 1.07)	1.03 (0.81, 1.35)	0.99 (0.86, 1.19)	0.035	0.084
UA, μmol/L	308.3 ± 95.7	337.1 ± 111.1	331.5 ± 90.0	0.846	0.590
Potassium, mmol/L	3.98 ± 0.45	4.04 ± 0.50	4.01 ± 0.37	0.414	0.971
CO_2CP, mmol/L	23.3 ± 4.3	24.1 ± 2.7	24.9 ± 2.4	0.206	0.080
IgA, g/L	2.60 ± 1.39	2.96 ± 1.01	2.36 ± 1.20	0.254	0.336
First-line treatment					
RAAS blockers, n (%)	35 (77.8)	40 (88.9)	31 (68.9)	0.157	0.340
Corticosteroid, n (%)	30 (66.7)	23 (51.1)	35 (77.8)	0.134	0.239
Immunosuppressive agents, n (%)	33 (73.3)	27 (60.0)	40 (88.9)	0.180	0.059
Cyclophosphamide, n (%)	14 (31.1)	8 (17.8)	23 (51.1)	0.141	0.054
Mycophenolate mofetil, n (%)	4 (4.9)	13 (28.9)	0	0.015	0.041
Tacrolimus, n (%)	11 (24.4)	5 (11.1)	17 (37.8)	0.098	0.172
Follow-up parameters					
Follow-up, months	45.9 (24.0, 72.0)	44.5 (31.3,57.8)	48.0 (32.2,66.3)	0.738	0.696
Primary endpoint, n (%)	11 (24.4)	18 (40.0)	6 (13.3)	0.046	0.178
Secondary endpoint, n (%)	11 (24.4)	24 (53.3)	9 (20.0)	0.005	0.612

Note: Values are presented as the mean ± standard deviation, median (interquartile range) or n (%). IgAN, immunoglobulin A nephropathy. MN, membranous nephropathy. cIgAN/MN, concurrent IgAN and MN. MAP, mean arterial pressure. UTP, urine total protein. WBC, white blood cell. Hb, hemoglobin. TP, total protein. Alb, albumin. TC, total cholesterol. TG, triglyceride. HDL, high density lipoprotein. LDL, low-density lipoprotein. eGFR, estimated glomerular filtration rate. BUN, blood urea nitrogen. UA, uric acid. Ca, calcium. CO_2CP, carbon dioxide combining power.

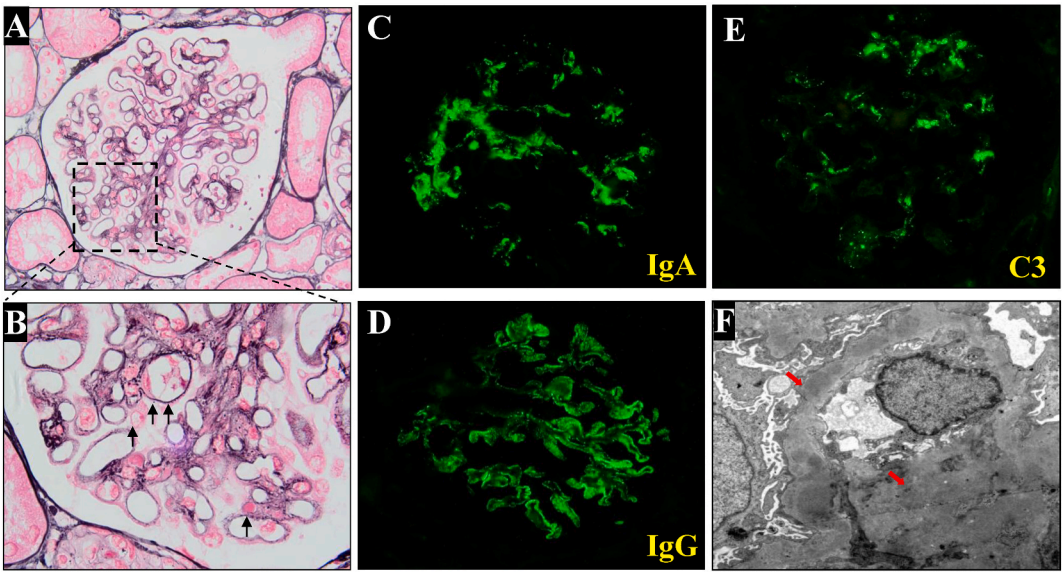

Fig. 2. Kidney biopsy pathological results of cIgAN/MN. (A, B) Light microscopy image showing thickened glomerular basement membranes, segmental glomerulosclerosis, spike-like projection, and fuchsin deposition in mesangial and subepithelial regions (arrows; periodic acid-silver methenamine, 400 × and 1000 ×). (C) Immunofluorescence staining for IgA (400 ×). (D) Immunofluorescence staining for IgG (400 ×). (E) Immunofluorescence staining for C3 (400 ×). (F) Electron microscopy showed thickening of glomerular basement membrane (600–700 nm), deposition of electron-dense material in subepithelial, intra-basement membrane and mesangial areas, and extensive fusion of foot processes (4000 ×).

3.3. Primary patient outcome

A total of 35 (25.9 %) patients reached the primary endpoint. No patient was lost to follow-up. Among cIgAN/MN patients, the median follow-up period was 45.9 (24.0, 72.0) months (Table 1), and 11 (24.4 %) experienced renal composite endpoints. Kaplan-Meier survival analysis showed that the estimated mean times of renal survival in the cIgAN/MN, IgAN, and MN groups were 76.7 (95 % confidence interval [CI] 66.8 – 86.6), 63.1 (95 % CI 53.1–73.1), and 85.0 (95 % CI 77.0–93.1) months, respectively. The cumulative 5-year renal survival rates of patients in the cIgAN/MN, IgAN, and MN groups were 67.5 %, 45.5 %, and 81.7 %, respectively. The difference in renal survival rates among the three groups of patients was statistically significant ($P = 0.005$) (Fig. 3A). Specifically, compared to IgAN, cIgAN/MN patients had a lower cumulative incidence rate of composite renal endpoints ($P = 0.044$), while there was no significant difference between cIgAN/MN and MN patients ($P = 0.211$).

3.4. Urinary protein remission

In addition, a total of 44 (32.6 %) patients failed to achieve CR or PR of urinary protein. We observed significant differences in the remission of proteinuria among the three groups ($P = 0.0006$) (Fig. 3B). The remission of urinary protein in the cIgAN/MN group was similar to that in the MN group ($P = 0.927$) but significantly better than that in the IgAN group ($P = 0.004$).

3.5. Risk factors affecting renal outcomes

Univariate Cox analysis showed that mean arterial pressure (MAP) ($P = 0.033$), BUN ($P = 0.047$), potassium ($P = 0.002$), serum IgA ($P = 0.036$), segmental glomerulosclerosis (S1) ($P = 0.024$), and stage III MN ($P = 0.001$) were associated with renal composite endpoints (Table 3). First, we included clinical measures in a multifactor Cox regression analysis (Model 1), and the results showed that MAP (hazard ratio [HR] = 1.051, 95 % CI 1.001–1.105, $P = 0.045$), potassium (HR = 14.782, 95 % CI 2.922–74.772, $P = 0.001$), and serum IgA (HR = 1.678, 95 % CI 1.154–2.440, $P = 0.007$) were independent risk factors affecting renal outcomes. The results of Model 2 showed that after adjusting for pathological score, potassium (HR = 14.350, 95 % CI 2.637–78.090, $P = 0.002$), serum IgA (HR = 1.870, 95 % CI 1.109–3.153, $P = 0.019$), S1 (HR = 11.965, 95 % CI 2.166–66.105, $P = 0.004$) and stage III MN (HR = 16.408, 95 % CI 2.385–112.883, $P = 0.004$) were independent risk factors affecting renal outcomes.

According to the MSRSM (Fig. S1), the optimal cutoff value for MAP was 98.33 mmHg, for potassium it was 4.40 mmol/L, and for serum IgA it was 2.82 g/L. Based on the optimal cutoff values, the cIgAN/MN patients were allocated into high and low groups. By Kaplan–Meier survival curve analyses, we found that patients with higher MAP (Fig. 4A), higher potassium (Fig. 4B), higher serum IgA (Fig. 4C), and S1 (Fig. 4D) were associated with adverse renal prognosis.

Table 2
Pathological features of patients with cIgAN/MN, IgAN, and MN.

Pathological features	cIgAN/MN (n = 45)	IgAN (n = 45)	MN (n = 45)	P (cIgAN/MN vs IgAN)	P (cIgAN/MN vs MN)
Light microscope					
Glomerulosclerosis ratio (%)	2.86 (0, 9.52)	23.53 (11.35, 38.70)	2.00 (0, 8.39)	< 0.001	0.416
Oxford score, n (%)					
M1	38 (84.4)	23 (51.1)	–	0.001	–
E1	13 (28.9)	8 (17.8)	–	0.213	–
S1	15 (33.3)	32 (71.1)	–	<0.001	–
T lesion scoring				0.076	–
T0	40 (88.9)	34 (75.6)	–		
T1	2 (4.4)	9 (20.0)	–		
T2	3 (6.7)	2 (4.4)	–		
C lesion scoring				0.122	–
C0	41 (91.1)	36 (80.0)	–		
C1	4 (8.9)	9 (20.0)	–		
C2	0 (0)	0 (0)	–		
Arteriole lesions, n (%)	30 (66.7)	36 (80.0)	31 (68.9)	0.153	0.822
Immunofluorescence					
IgA in mesangial area				0.350	<0.001
0	0 (0)	0 (0)	40 (88.9)		
1	1 (2.2)	0 (0)	5 (11.1)		
2	17 (37.8)	12 (26.7)	0 (0)		
3	27 (60.0)	32 (73.3)	0 (0)		
4	0 (0)	1 (2.2)	0 (0)		
IgG in capillary loops				<0.001	<0.001
0	1 (2.2)	40 (88.9)	0 (0)		
1	13 (23.9)	2 (4.4)	3 (6.7)		
2	21 (46.7)	2 (4.4)	13 (28.9)		
3	10 (22.2)	1 (2.2)	29 (64.4)		
IgM in capillary loops				<0.001	<0.001
0	10 (22.2)	29 (64.4)	32 (71.1)		
1	16 (35.6)	10 (22.2)	7 (15.6)		
2	17 (37.8)	6 (13.3)	4 (8.9)		
3	2 (4.4)	0 (0)	2 (4.4)		
C3 in capillary loops				0.007	0.023
0	6 (13.3)	11 (24.4)	17 (37.8)		
1	22 (48.9)	13 (28.9)	18 (40.0)		
2	16 (35.6)	11 (24.4)	8 (17.8)		
3	1 (2.2)	10 (22.2)	2 (4.4)		
Pathological stage of MN				–	0.005
Stage I	29 (64.4)	–	14 (31.1)		
Stage II	12 (26.7)	–	26 (57.8)		
Stage III	4 (8.9)	–	5 (11.1)		
Stage IV	0 (0)		0 (0)		

Note: Values are presented as the median (interquartile range) or n (%). IgAN, immunoglobulin A nephropathy. MN, membranous nephropathy. cIgAN/MN, concurrent IgAN and MN. M1, mesangial hypercellularity. E1, endocapillary hypercellularity. S1, segmental glomerulosclerosis. Tubular atrophy/interstitial fibrosis ≤25 % (T0), 26%–50 % (T1), >50 % (T2). C0, no crescents; C1, crescents in less than one fourth of glomeruli; C2, crescents in over one fourth of glomeruli.

4. Discussion

With the gradual recognition of concurrent pathologic types in kidney disease, an increasing number of studies have been focused on the pathogenesis and prognosis of the disease. The present study in an 8-year cohort evaluated the renal prognosis and clinical outcomes in IgAN, MN, and cIgAN/MN patients. To the best of our knowledge, this study is the first to focus on the long-term prognosis of the three groups and the risk factors for cIgAN/MN patients.

The prognosis of patients with cIgAN/MN or separate pathological types has always been the focus of attention. From our results, the clinical manifestations of cIgAN/MN disease are similar to MN but less severe than IgAN. This is consistent with previous studies [7, 8]. At the same time, in terms of outcomes, the prognosis of cIgAN/MN patients was significantly better than that of IgAN patients but similar to MN patients, both from renal outcomes and urinary protein endpoints. Currently, cohorts from multiple countries and regions have proven that the risk of ESRD in MN is significantly lower than that in IgAN [18]. Chen et al. [7] also confirmed that cIgAN/MN has unique renal histopathology, but the prognosis does not seem to be worse than MN. The results of our study are consistent with these conclusions. In this study we confirmed that the prognosis of cIgAN/MN patients was significantly better than that of IgAN patients, which may be related to the lower rate of glomerulosclerosis, earlier detection of symptoms, and better response to treatment. Due to the more MN-similar pathological types and clinical manifestations, the treatment of cIgAN/MN was often similar to MN, with supportive treatment as the main treatment for mild cases and corticosteroids plus cyclophosphamide as the main treatment for severe cases. In addition, proteinuria is a well-known adverse prognostic factor in CKD, and effective remission of

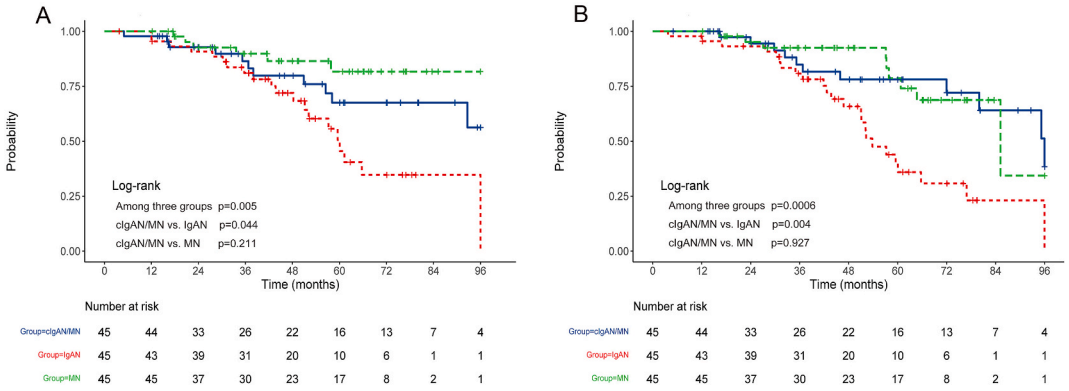

Fig. 3. Kaplan-Meier survival curves for free of combined events of different groups. (A) Cumulative poor event-free renal survival rate. (B) Cumulative incidence of urinary protein PR or CR. IgAN, immunoglobulin A nephropathy. MN, membranous nephropathy. cIgAN/MN, concurrent IgAN and MN.

proteinuria is an important reason for improving the prognosis of CKD [19]. The remission rate of UTP in cIgAN/MN was significantly higher than that in IgAN, which may contribute to the beneficial prognosis of cIgAN/MN patients. However, despite the different treatment options, no significant difference in adverse prognosis between cIgAN/MN and MN only was exhibited. The implication is that the similar pathology and clinical presentation may contribute to this observation. Results from further randomized clinical trials will help in the selection of treatment options for cIgAN/MN patients to improve prognosis.

Previous studies have built multiple prognostic models to predict the outcome of IgAN and MN patients, of which the main independent risk factors include decreased eGFR, baseline UTP, hypertension, hyperuricemia, and pathological scores [20,21]. Although controversy remains about whether the addition of histologic variables can improve clinical risk models for the early prediction of disease progression [22], the MEST-C score is widely used for classification based on outcome evidence [14]. Clinical studies on IgAN found that the addition of the MEST-C variable can further improve the performance of clinical models compared with models without Oxford score variables [22–24]. Therefore, we innovatively added the MEST-C score and the characteristic pathological change score of MN into the cIgAN/MN prediction model. IgAN and MN patients with focal segmental sclerosis lesions tend to have more serious pathological manifestations, including more severe glomerulosclerosis, interstitial infiltration, interstitial fibrosis and tubular atrophy, which indicate the occurrence of adverse outcomes [25–27]. From our results, a consistent conclusion was also observed in cIgAN/MN patients. In addition, we found that the stage of membranous nephropathy (stage III) may predict a poor outcome. Because of the small number of patients, we did not take this as the main conclusion. However, this does not detract from the critical role of pathological scores in our prediction model.

Serum potassium was identified as an independent risk factor for the prognosis of cIgAN/MN. The incidence of hyperkalemia was found to be significantly higher in CKD patients [28]. In addition, the likelihood of developing hyperkalemia exhibits a positive correlation with declining renal function in individuals with CKD and is associated with a poor prognosis [29]. Therefore, we conceive that higher potassium is predictive of more aggressive disease in patients with cIgAN/MN, and it is necessary to strictly manage serum potassium in this group of patients. In general, potassium intake for CKD stage 1 or 2 patients is recommended to be similar to that of the healthy population (2700–3000 mg/day), while dietary potassium intake should be limited to less than 2000 mg/day for stage 3b patients and less than 1500 mg/day for stage 4 patients [30].

In our cIgAN/MN cohort, serum IgA showed strong predictive significance for renal outcomes in both models. In IgAN, elevated serum IgA levels may correlate with disease activity. Therefore, high serum IgA levels may also be strongly associated with disease severity in cIgAN/MN. In a Japanese cohort, multivariate analysis did not show the prognostic significance of serum IgA level, but a cutoff of >315 mg/dL could predict the diagnosis of patients with IgAN before biopsy [31]. In children with IgAN, elevated serum IgA at baseline may be associated with the Oxford classification (mesangial hypercellularity and S1) [32]. Additionally, the IgA/C3 ratio has a role in predicting the diagnosis of IgAN [33]. Therefore, more attention should be given to the prognosis of cIgAN/MN patients with high serum IgA. In the future, it is hoped that a larger cohort will further validate the value of serum IgA in the diagnosis, monitoring, and prognostication of cIgAN/MN.

The current study also found that MAP is a meaningful variable in models of clinical data in cIgAN/MN. In IgAN patients, blood pressure (BP) is one of the most accessible risk factors for predicting renal prognosis [34]. Meanwhile, the support vector machine model including the MAP variable has potential practical value in predicting the prognosis of IgAN patients with focal crescent shape [35]. In MN patients with hypertension, the cumulative renal survival rate is lower than that of patients without hypertension, indicating that diastolic blood pressure may be an independent risk factor for prognosis [36]. Therefore, physicians generally prioritize BP control to preserve kidney function and lower the risk of cardiovascular events and mortality in CKD [37]. Since the Systolic Blood Pressure Intervention Trial (SPRINT), intensive blood pressure control has become a consensus in the treatment guidelines for various types of nephropathies, although the specific target value for blood pressure reduction remains controversial [38,39]. As seen from the MDRD (modification of diet in renal disease) study [40], after strict control of BP, CKD patients with urinary protein>1 g/d have greater renal benefits. A meta-analysis similarly found that intensive BP control (<130/80 mmHg) attenuated CKD progression in

Table 3
Predictors of renal combined events in cIgAN/MN patients.

Varibales		Univariate analysis			Multivariate analysis ([a]Model 1)			Multivariate analysis ([b]Model 2)		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value
MAP		1.054	1.004–1.105	0.033	1.051	1.001–1.105	0.045	Not included		
BUN		1.272	1.003–1.613	0.047	Not included			Not included		
eGFR		1.00	0.972–1.028	0.998	Not included			Not included		
UTP		0.998	0.997–1.000	0.738	Not included			Not included		
Alb		1.037	0.964–1.115	0.332	Not included			Not included		
K		9.381	2.219–39.652	0.002	14.782	2.922–74.772	0.001	14.350	2.637–78.090	0.002
IgA		1.435	1.023–2.013	0.036	1.678	1.154–2.440	0.007	1.870	1.109–3.153	0.019
Treatment methods	Supportive therapy	Ref.		0.903	Not included			Not included		
	CS	1.615	0.100–26.213	0.736						
	IMMS	2.334	0.240–22.662	0.465						
	CS + IMMS	1.987	0.237–16.674	0.527						
S1		4.735	1.229–18.241	0.024	Not included			11.965	2.166–66.105	0.004
Pathological stage of MN	Stage I	Ref.		0.006	Not included			Ref.		0.018
	Stage II	1.862	0.441–7.858	0.397				2.428	0.436–13.531	0.312
	Stage III	13.767	2.742–64.132	0.001				16.408	2.385–112.883	0.004

Note: MAP, mean arterial pressure. BUN, blood urea nitrogen. eGFR, estimated glomerular filtration rate. UTP, urinary total protein. Alb, albumin. K, potassium. CS, corticosteroids alone. IMMS, immunosuppressants alone. S1, segmental glomerulosclerosis. Ref, reference.

[a] Model 1 was adjusted for MAP, BUN, eGFR, UTP, K, and IgA.

[b] Model 2 was adjusted for MAP, BUN, IgA, K, and Histological lesion scoring.

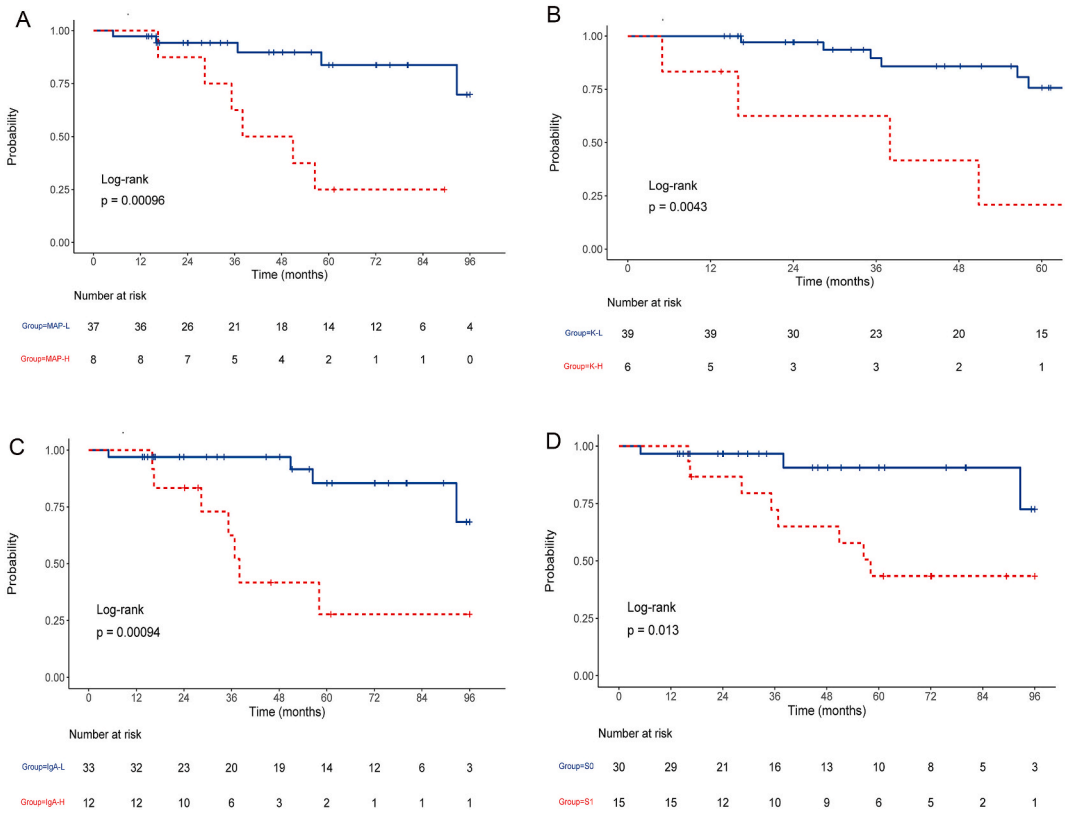

Fig. 4. Survival curve of cIgAN/MN patients under different factors. (A) MAP, mean arterial pressure. (B) K, potassium. (C) serum IgA. (D) S1, segmental glomerulosclerosis.

nondiabetic patients and significant proteinuria [41]. Therefore, we emphasize the importance of intensive blood pressure control in cIgAN/MN patients to improve outcomes.

Attaining lower proteinuria tends to predict better renal survival in patients with MN [42,43]. However, we did not observe a predictive effect of urinary protein on disease outcomes in cIgAN/MN patients. This may be a point of difference between the two diseases. In addition, BUN is a stronger independent factor of the occurrence of ESRD, which was confirmed in IgAN [44] and MN [42]. Elevated BUN level is associated with conditions such as hypovolemia, severe histopathology, and acute renal hypoperfusion [45], highlighting the predictive value of BUN in assessing kidney function. Our results are consistent with previous studies showing that younger age, higher uric acid, and decreased Hb levels are risk factors for aggressive IgAN. Thus, we consider that BUN is still a key prognostic indicator of cIgAN/MN, although it is only meaningful in univariate analysis.

The constraints of our present design studies are substantial. First, the relatively modest sample size is the main limitation, which will affect the generalizability of the results. We need more multicenter research with a greater number of participants to provide us with stronger evidence. However, we strictly followed the screening criteria, enhancing the repeatability of our research. Moreover, we collected data retrospectively through the electronic medical record system, and due to the long follow-up time, some data, such as PLA2R results, are reliable, so the conclusions may be affected by unknown confounding factors. To this end, we performed multivariate analysis to adjust the important clinical parameters, lowering the possibility of bias. Finally, we only collected medication regimen information on baseline treatment and were unable to assess treatment changes and effects during follow-up. Although treatment is not a risk factor in our models, more treatment-specific studies may be needed.

5. Conclusion

This retrospective study evaluated renal prognosis and clinical outcomes in IgAN, MN, and cIgAN/MN groups and evaluated risk factors affecting long-term renal outcomes in cIgAN/MN patients. The prognosis of cIgAN/MN patients may exhibit an intermediate pattern between IgAN and MN, leaning towards being more similar to MN in certain aspects. During the long-term clinical follow-up of the cIgAN/MN cohort, we observed that blood pressure, serum IgA, potassium, and segmental glomerulosclerosis may be predictive of the rapid progression of renal endpoints. These findings have the potential to improve clinical decision-making in medical practice, while well-designed studies are warranted for further verification.

Data availability

Data sharing was not applicable to this study as the data may contain potentially sensitive patient information. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

This study was approved by the Ethics Committee of Xijing Hospital and conducted following the Helsinki Declaration (ethical number: KY20213027-1). Due to the retrospective design, the Ethics Committee waived the requirement for informed consent from eligible patients.

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CRediT authorship contribution statement

Yunlong Qin: Writing - original draft, Software, Methodology, Formal analysis, Data curation. **Zixian Yu:** Writing - review & editing, Software, Data curation. **Hao Wu:** Software. **Anjing Wang:** Methodology, Data curation. **Fang Wang:** Writing - original draft, Validation, Software. **Di Wang:** Writing - review & editing, Methodology. **Qing Jia:** Investigation, Formal analysis, Data curation. **Jinguo Yuan:** Writing - review & editing, Writing - original draft. **Yan Xing:** Writing - review & editing, Writing - original draft. **Yumeng Zhang:** Writing - review & editing. **Jin Zhao:** Writing - review & editing, Formal analysis, Data curation, Conceptualization. **Shiren Sun:** Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23436.

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