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ORIGINAL RESEARCH

The Correlation Between Podocyte Senescence and the Clinicopathology in Elderly Patients with IgAN

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Purpose: IgAN is a common primary glomerular disease, and age may affect its clinical manifestations and progression. However, age-related differences in elderly IgAN, especially the role of podocyte senescence and the cGAS-STING pathway in elderly IgAN patients, remain incompletely understood.

Patients and Methods: This retrospective study analyzed 1012 renal biopsy-confirmed IgAN patients from January 2014 to January 2024, categorized into elderly (≥60 years, n=119) and younger (18–60 years, n=893)) groups after exclusion. Clinical, laboratory, and pathological data were collected. Kaplan-Meier survival analysis and Cox proportional hazard models were used to evaluate prognostic factors. Expression of the cGAS-STING pathway in renal tissues was detected to explore its association with podocyte injury. SASP in serum was detected by ELISA and qPCR.

Results: Compared with the young IgAN group, the elderly IgAN group had higher levels of 24-hour urinary protein, urea and creatinine; lower hemoglobin and albumin; more severe tubular atrophy/interstitial fibrosis (T1/2 lesions, 47.1% vs. 23.9%); lower IgA immunofluorescence intensity; and more severe podocyte fusion. Kaplan-Meier analysis showed poorer renal outcomes in the elderly IgAN group ($P<0.05$). Multivariate Cox regression identified podocyte fusion (>50%) as an independent prognostic factor in the elderly IgAN group (HR=5.72, $P=0.011$) but not in the young IgAN group.The cGAS-STING pathway is highly expressed in the podocyte of IgAN, especially in the elderly, SASPs in serum, such as IL-6, IL-10, were also highly expressed in the elderly IgAN group, indicating that its activation is related to severe podocyte fusion, elevated proteinuria, and impaired renal function.

Conclusion: Elderly IgAN patients exhibit distinct clinicopathological features dominated by chronic lesions and podocyte injury. Severe podocyte fusion (>50%) is a critical independent prognostic factor for this population. The cGAS-STING pathway may mediate age-related podocyte senescence and injury, representing a potential therapeutic target for elderly IgAN patients.

Keywords: immunoglobulin A nephropathy, podocyte senescence, cGAS-STING, elderly patients, clinical studies

Introduction

Immunoglobulin A nephropathy(IgAN), characterized by the deposition of IgA immune complexes in the glomerular mesangium, is recognized as one of the most prevalent primary glomerular diseases worldwide.[1,2] It poses a significant threat to renal health, as a considerable proportion of patients progress to end-stage renal disease (ESRD) over time.[3]

While elderly IgAN patients often present with distinct and more severe clinical features,[4] the specific age-related differences in renal pathology and their impact on disease progression remain unclear.Podocyte fusion is a key driver of proteinuria and renal functional decline, yet its age-specific prognostic value in elderly patients has not been systematically evaluated. Moreover, podocyte injury has emerged as a key player in the pathogenesis of proteinuria and renal

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function decline in various glomerular diseases,[5] including IgAN podocyte fusion, a hallmark of podocyte injury, has been linked to massive proteinuria, but its role in the prognosis of IgAN, especially in the context of aging, has not been systematically explored. Whether podocyte fusion acts as an age-specific prognostic factor, particularly in elderly IgAN patients, remains an unanswered question.

In parallel, cellular senescence has seemed to be a potential link between aging and organ dysfunction, and the cGAS-STING pathway has been identified as a key regulator of senescence.[6] Activation of this pathway is known to drive cellular aging processes, but its involvement in podocyte injury in IgAN, particularly in the context of age-related differences, has not been investigated.As a key feature of senescent cells, senescence-associated secretory phenotype (SASP) is closely linked to the cGAS-STING pathway.[7] Given that senescence may aggravate podocyte damage, exploring whether the cGAS-STING pathway mediates age-related podocyte senescence and injury by SASP in IgAN could uncover potential therapeutic targets.

Method

Participants

This study included patients with IgAN who were diagnosed by renal biopsy at Hangzhou Hospital of Traditional Chinese Medicine from January 2014 to January 2024. The diagnosis of IgAN depended on the presence of IgA deposits in the glomerular mesangium as shown by immunofluorescence and electron-dense deposits under electron microscopy. After applying the exclusion criteria for secondary diseases, a follow-up period of less than 6 months, and incomplete clinical data, we finally enrolled 1012 IgAN patients, including 119 patients over 60 years old and 893 patients aged between 18 and 60 years. Therefore, we divided them into the elderly IgAN group (n=119) and the young IgAN group (n=893) based on whether their age was over 60 years. In adherence to the Declaration of Helsinki, this retrospective study received ethical approval from the Ethics Committee of Hangzhou Hospital of Traditional Chinese Medicine (Approval Number: 2024KLL230). The requirement for obtaining informed consent was waived by the ethics committee because the research involved the analysis of existing anonymized data, and obtaining consent was impracticable without compromising the validity of the study.

We have compiled the baseline characteristics of the excluded patients and compared them with the included cohort. This comparison is presented in Supplementary Table 1. We further stratified the excluded patients into elderly (≥60 years old) and young groups (<60 years old) and compared their baseline characteristics (Supplementary Table 2). Significant differences were observed in key variables, including 24-hour urinary protein, serum creatinine, and severe podocyte fusion (>50%), which were consistent with the baseline patterns in the included cohort.

Data Collection

At the time of renal biopsy, the following baseline clinical and laboratory data were collected by retrospectively reviewing electronic medical record (EMR) system and renal pathology database: age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), 24-hour urinary protein (24 h UP), serum creatinine(SCr), serum uric acid(SUA), urea, hemoglobin(Hb) as well as albumin(ALB). Renal function was evaluated by applying a modified equation to estimate the glomerular filtration rate (eGFR). Hypertension was diagnosed in patients with a resting SBP ≥ 140 mmHg and/or DBP≥90 mmHg, or based on a self-reported history of hypertension. The diabetes was diagnosed if any of the following criteria were met: a fasting blood glucose level ≥ 7.0 mmol/L, a 2-hour oral glucose tolerance test (OGTT) value ≥ 11.1 mmol/L, or a glycated hemoglobin (HbA1c) level ≥ 6.5%.[8] The history of alcohol consumption was collected through the review of electronic medical records combined with self-reports of patients.The same method was used to collect data on patients with a history of regular smoking (defined as smoking ≥1 cigarette per day for a continuous period of ≥3 months). The immunofluorescence intensities of IgA and C3 were graded on a scale from - to 4+. Grades of 3+ and 4+ were defined as strong positivity and were statistically analyzed. The IgM immunofluorescence intensity was classified into - to 3+ three grades, with 2+ to 3+ defined as strongly positive and statistically analyzed. The positive proportions of IgG and C4 immunofluorescence were also statistically analyzed. Histological lesions are graded by qualified pathologists according to the Oxford scale (M: mesangial cell proliferation; E:

intracellular cell proliferation in capillaries; S: glomerular sclerosis; T: tubular atrophy and interstitial fibrosis; C: crescentic cells or fibroblasts). The degree of podocyte fusion was observed under an electron microscope, and the data of podocyte fusion degree greater than 50% were statistically analyzed. This study collected the treatment of all included patients from the first treatment after the diagnosis of IgAN by renal puncture to the data collection date. The treatment included Glucocorticoids(GC), angiotensin converting enzyme inhibitor(ACEI), angiotensin receptor blocker-(ARB) and sodium-dependent glucose transporters 2(SGLT2) without distinction of specific drug types and doses.

Outcomes

The combined endpoints of kidney outcome were eGFR< 15 mL/min/1.73m^2, doubling of serum creatinine from baseline, treatment by dialysis, or requiring kidney replacement treatments.

Statistical Analyses

Categorical variables are presented as frequencies (percentages) and analyzed using the chi-squared test or Fisher's exact test. Continuous variables are presented as the mean ± standard deviation (SD) or median (interquartile range) depending on their characteristics, and group comparisons are performed using the *t* test, one-way ANOVA, or Kruskal–Wallis test. To estimate the cumulative incidence of kidney outcomes, we employed Kaplan-Meier survival analysis and compared the survival distributions among different groups using the Log rank test. The effects of demographic and clinicopathological characteristics on the risk of reaching the endpoints were assessed by univariate followed by multivariate Cox proportional hazards models (with a forward: conditional method for variable selection).

To further examine whether the prognostic impact of podocyte fusion was modified by age, a pre-specified subgroup analysis was conducted. Within each age stratum, the effect of podocyte fusion on prognosis was analyzed separately. Kaplan-Meier survival curves were generated for severe and mild fusion groups within both the elderly and young cohorts, and differences were assessed using the Log rank test. Hazard Ratios (HRs) and 95% confidence intervals were calculated using Cox proportional hazards models, stratified by age group.Statistical significance was set at a two-tailed $P < 0.05$. The entire dataset was analyzed with IBM SPSS Statistics software (version 26.0).

cGAS-STING Immunohistochemistry

First, immerse the frozen renal tissue sections obtained from clinical specimens in 1×PBS for 10 minutes. Then, incubate the sections with mouse anti-human cGAS antibody (1:100, Immunoway) and rabbit anti-human pSTING antibody (1:100, Invitrogen) at 4°C overnight. Next, incubate the sections with fluorescent secondary antibodies (rabbit anti-mouse, 1:200/594; mouse anti-rabbit, 1:200/488, Cohesion Bioscience) at 37°C in the dark for 1 hour. Subsequently, counterstain the cell nuclei with DAPI (Beyotime) for 15 minutes. Finally, mount the sections with anti-fluorescence quencher (Beyotime) and image them using an Olympus fluorescence microscope.After each step, wash the sections with 1×PBS for 3 times.

Detection of SASP in Serum

An enzyme-linked immunosorbent assay (ELISA) was employed to quantify the concentrations of IL-6 and IL-10 in the serum samples obtained from IgAN patients. The initial step involved coating Corning™ Costar™ 9018 plates with the capture antibody solution, which was followed by an overnight incubation at 4°C. Subsequently, the wells were blocked by adding ELISA/ELISPOT diluent and incubating the plate for one hour at room temperature. Add the standard substance and the patient's serum in sequence for 2 hours. Add Ddiluted Detection Antibody to all wells for 1 hour. Add diluted Streptavidin-HRP for 30 minutes. Add 1X TMB Solution, for 15 minutes. Each of the above step, aspirate wells and at least wash 3 times Wash Buffer.Allowing time for soaking (~1 minute) during each wash step increases the effectiveness of the washes. Blot plate on absorbent paper to remove any residual buffer. Finally add Stop Solution, read plate at 450 nm.

The qPCR was also used to detected the IL-6 and CXCL-10 in the serum of the patients with IgAN.After extracting peripheral blood mononuclear cells (PBMC) from the patient, DNA was extracted and purified using leukocyte lysate (Promega, catalog number: PR-A7951). Real-time fluorescence quantitative PCR was performed using 20ng DNA as the

template. ChamQ Universal SYBR qPCR Master Mix (Nanjing Novezan, catalog number: Q711-02) was adopted. The reaction procedure was as follows: Pre-denaturation at 94°C for 5 minutes, denaturation at 94°C for 30 seconds, annealing at 60°C for 30 seconds, extension at 72°C for 40 seconds, 50 cycles, extension at 65°C for 5 seconds.

Result

Baseline Characteristics of All Patients

A total of 3481 patients diagnosed with IgAN in our medical center between January 2014 and January 2024 were primarily included. The initial patient population was refined through the application of the following exclusion criteria: secondary IgA nephropathy, follow-up time less than 6 months, and absence of key baseline data. This process yielded a final analytic cohort of 1012 patients, with a mean age of 43.89 ± 11.85 years. A female predominance (59%) was noted. Patients were followed for a mean duration of 35.04 ± 19.37 months (over 60 years old)(Figure 1). The demographic data of each group are shown in Table 1. The proportion of male patients in the elderly IgAN group was higher (46.2%). At the time of kidney biopsy, elderly IgAN group had a higher incidence of hypertension (16.8%),but the difference was not significant. Meanwhile, elderly patients more frequently had a alcohol consumption (15.1%) and smoking history (20.2%). As for clinicalpathological data, The 24h UP differed significantly among two groups, with the elderly IgAN group having the higher level (1.73g/24h). Compared with the young IgAN group, the levels of SUA, SCr and urea in the elderly IgAN group were higher, while the levels of Hb and ALB were lower, and all were statistically significant.

We further compared the renal pathological changes of the two groups of patients. The results showed that in elderly patients, the proportion of T1/2 in the elderly IgAN group was 47.1%, which was significantly higher than that in the young IgAN group (23.9%). However, there were no significant differences among the groups of E,S, M, C1/2 scores. Meanwhile, immunofluorescence examination showed that the proportion of strongly positive IgA in elderly patients was 71.4%, significantly lower than that in younger patients. This suggests that the renal lesions of elderly patients in the IgAN group are mainly chronic. Active renal damage caused by immune complex deposition is not the main factor leading to disease progression in elderly patients with nephropathy.

In IgAN, podocyte injury is an important cause of massive proteinuria. We further observed the degree of podocyte fusion in each group of patients through electron microscopy. The results showed that the proportion of patients with podocyte fusion greater than 50% in the elderly IgAN group was significantly higher than that in young IgAN groups. Therefore, we suspect that podocyte injury may be an important cause of massive proteinuria and disease progression in elderly patients.

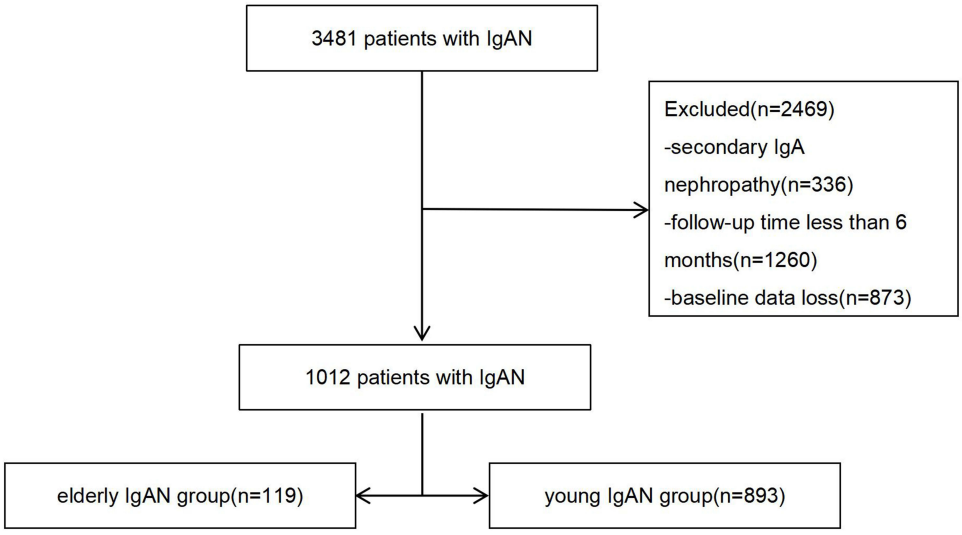

Figure 1 Study flow chart.The patients were recruited into the study according to the flow chart shown.

Table 1 Clinicopathological Manifestations and Laboratory Data of the IgAN Patients at Baseline

Characteristics	Total (n=1012)	Young IgAN Group (n=893)	Elderly IgAN Group (n=119)	P
Male (%)	415 (41.0)	360 (40.3)	55 (46.2)	<0.05
Age (years)	43.89±11.85	41.07±9.38	65.08±4.91	<0.05
SBP	125.33±21.01	124.11±20.14	134.45±24.95	<0.05
DBP	78.90±13.20	78.93±13.29	78.67±12.52	0.84
Hypertension (%)	136 (13.4)	116 (13.0)	20 (16.8)	0.25
Diabetes (%)	2 (0.2)	2(0.2)	0 (0)	0.61
Alcohol consumption (%)	55 (5.4)	37 (4.1)	18 (15.1)	<0.05
Smoking (%)	112 (11.1)	88 (9.9)	24 (20.2)	<0.05
Hb	127.57±18.92	128.47±18.66	120.83±19.58	<0.05
ALB	37.87±4.41	38.17±4.25	35.62±4.92	<0.05
24h-UP	1.36±1.59	1.32±1.55	1.73±1.82	<0.05
SUA	367.95±101.93	366.24±102.00	380.76±100.88	<0.05
SCr	94.86±61.83	91.87±58.36	117.29±80.21	<0.05
Urea	6.12±3.03	5.90±2.82	7.80±3.91	<0.05
M(1,%)	1011 (99.9)	892 (99.9)	119 (100)	0.71
E(1%)	398 (39.3)	357 (40.0)	41 (34.5)	0.25
S(1,%)	824 (81.4)	731 (81.9)	93 (78.2)	0.33
T(1/2,%)	269 (26.6)	213 (23.9)	56 (47.1)	<0.05
C(1/2,%)	674 (66.6)	598 (67.0)	76 (63.9)	0.50
Podocyte fusion>50%	130 (12.8)	82 (9.2)	48 (40.3)	<0.05
IgA (3+/4+,%)	826 (81.6)	741 (83.0)	85 (71.4)	<0.05
IgG (+,%)	343 (33.9)	309 (34.6)	34 (28.6)	0.19
IgM (2+/3+,%)	194 (19.2)	173 (19.4)	21 (17.6)	0.65
C3 (3+/4+,%)	351 (34.7)	319 (35.7)	32 (26.9)	0.06
C4 (+,%)	47 (4.6)	41 (4.6)	6 (5.0)	0.83
ARB	790 (78.1)	694 (77.7)	96 (80.7)	0.46
ACEI	167 (16.5)	159 (17.8)	8 (6.7)	<0.05
SGLT2	107 (10.6)	101 (11.3)	6 (5.0)	<0.05
GC	275 (27.2)	245 (27.4)	30 (25.2)	0.61
Follow-up time	35.04±19.37	34.94±19.20	35.85±20.69	0.78

Notes: The final cohort consisted of patients with complete data for all variables listed. Patients with any missing baseline data were excluded.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ALB, albumin; 24h-UP, 24-hour urine protein; SUA, serum uric acid; SCr, serum creatinine; M, mesangial proliferation; E, endocapillary proliferation; S, segmental glomerulosclerosis; C, crescents; T, tubular atrophy/interstitial fibrosis; GC, glucocorticoids; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SGLT2, sodium-dependent glucose transporters 2.

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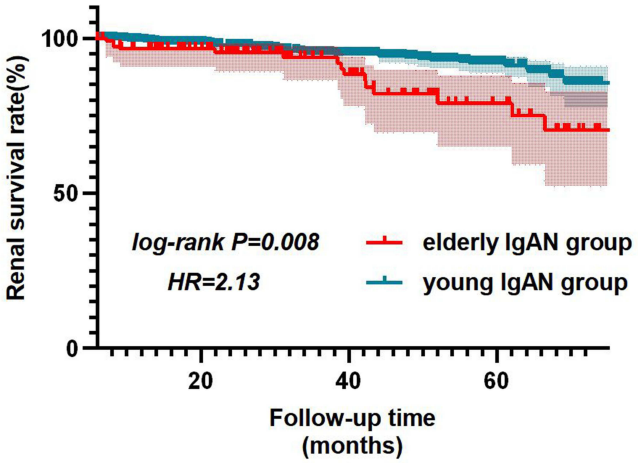

Figure 2 Kaplan-Meier curves of kidney survival according to age. The elderly IgAN group had a significantly poorer renal survival compared to the young group (HR=2.13, P<0.05).

Risk Factors for Kidney Outcomes

The Kaplan-Meier survival analysis was performed based on the different groupings to further ascertain prognostic indicators, with the results presented in Figure 2. A significant difference in survival was observed between the two aged-groups (HR=2.13, *P*<0.05), which also comes to be an important evidence that age is an indispensable actor affecting prognosis.

Univariate and multivariate Cox proportional hazard regression models were performed to analyze the relationship between clinicopathological parameters and kidney outcomes. As shown in Table 2, Several risk and protect factors had

Table 2 Prediction of Renal Outcomes in the IgAN Was Carried Out by Cox-Regression Analysis

Characteristics	Total (n=1012)		Young IgAN Group (n=893)		Elderly IgAN Group (n=119)	
	HR	*P*	HR	*P*	HR	*P*
Male	3.08	<0.001	3.85	<0.001	1.91	0.22
Age	1.04	<0.001	1.04	0.011	1.02	0.68
SBP	1.03	<0.001	1.04	<0.001	1.02	0.10
DBP	1.04	<0.001	1.05	<0.001	1.01	0.77
Hypertension	1.26	0.574	1.03	0.953	1.35	0.64
Alcohol consumption	2.19	0.046	3.57	0.004	1.33	0.71
Smoking	2.20	0.012	2.71	0.006	1.09	0.90
Hb	0.97	<0.001	0.97	0.002	0.95	<0.001
ALB	0.87	<0.001	0.85	<0.001	0.92	0.04
24h-UP	1.41	<0.001	1.42	<0.001	1.35	<0.001
SUA	1.01	<0.001	1.01	<0.001	1.01	0.03
SCr	1.01	<0.001	1.01	<0.001	1.01	<0.001
Urea	1.20	<0.001	1.20	<0.001	1.19	<0.001

(*Continued*)

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Table 2 (Continued).

Characteristics	Total (n=1012)		Young IgAN Group (n=893)		Elderly IgAN Group (n=119)	
	HR	*P*	HR	*P*	HR	*P*
E	1.12	0.679	1.04	0.915	1.66	0.35
S	13.01	0.011	0.04	8.498	28.43	0.23
T	164.67	<0.001	138.32	<0.001	78.95	0.04
C	2.05	0.026	1.63	0.175	4.33	0.05
Podocyte fusion>50%	5.64	<0.001	6.23	<0.001	4.69	0.01
IgA	0.45	0.004	0.69	0.314	0.24	0.01
IgG	0.36	0.012	0.27	0.012	0.76	0.67
ARB	0.25	<0.001	0.19	<0.001	0.39	0.07
ACEI	0.18	0.004	0.15	0.008	0.04	0.41
GC	1.47	0.161	0.61	0.114	0.88	0.82

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ALB, albumin; 24h-UP, 24-hour urine protein; SUA, serum uric acid; SCr, serum creatinine; E, endocapillary proliferation; S, segmental glomerulosclerosis; C, crescents; T, tubular atrophy/interstitial fibrosis; GC, glucocorticoids; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

been found by univariate Cox proportional hazard regression in different age groups. Hb, ALB had shown the statistical significance in both two groups as two protect factors, while 24h UP, SUA, SCr, urea and Mestc score T came to be the risk factors. Except for these recognized independent risk factor, podocyte fusion has attracted our attention. In elderly IgAN group, podocyte fusion emerged as a notable risk factor, showing a strong association with disease progression (HR=4.69) with statistically significant. To further clarify the impact of podocyte fusion on prognosis in different age groups, we compared the effects of podocyte fusion on prognosis in elderly patients and young patients.The Kaplan-Meier survival analysis showed the prognosis of the severe podocyte (podocyte fusion >50%) fusion group was worse than that of the mild one no matter in which age group, but as the elderly IgAN group has a higher HR of 4.65, podocyte fusion especially posed a greater risk to the prognosis of elderly patients (Figure 3).Since the degree of proteinuria is closely associated with podocyte injury,we compared podocyte fusion between elderly and young IgAN patients with severe proteinuria to clarify the independent role of senescence as a risk factor for podocyte injury.Results showed that

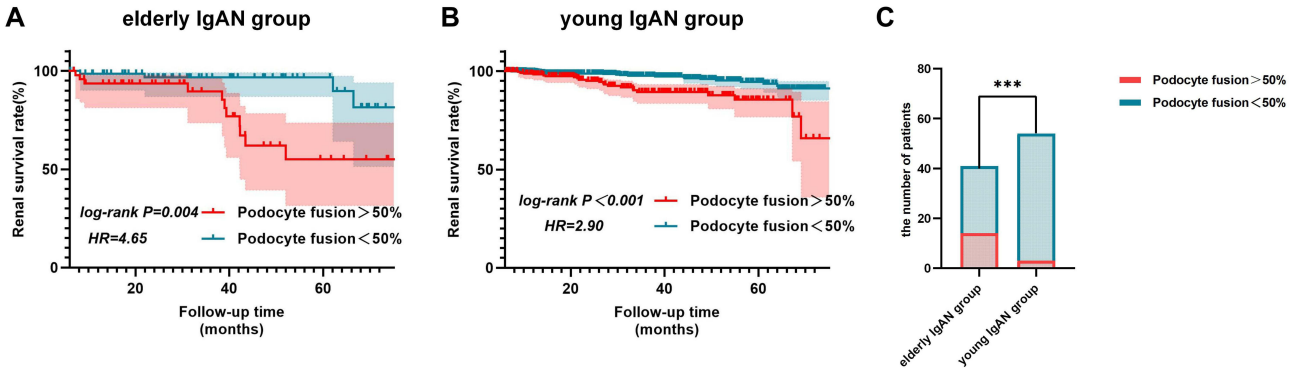

Figure 3 Kaplan-Meier curves of kidney survival according to the degree of podocyte fusion. (**A**) elderly IgAN group, (**B**) young IgAN group. Podocyte fusion (>50%) affects renal survival in IgAN, with a stronger effect in elderly (HR=4.65) than young (HR=2.90) patients. (**C**) Comparison podocyte fusion between elderly and young IgAN patients with severe proteinuria,***stands for P<0.001.

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Table 3 Multivariate Cox Regression Analysis Podocyte Fusion and Renal Outcomes

Group	Model	
	HR	*P*
Young IgAN group	2.25	0.119
Elderly IgAN group	5.72	0.011

Notes: The model was adjusted for gender, alcohol consumption, clinic factors (24-hour urine protein, hemoglobin, albumin, blood uric acid, urea, eGFR), Mestc score (S,T,C), immunofluorescence (IgA,C4), podocyte fusion and treatment.

among patients with 24h UP > 3g, the proportion of elderly IgAN patients with podocyte fusion > 50% was still significantly higher than that of young IgAN patients.

The multivariate Cox regression models were performed to further explore the factors influencing the prognosis of IgAN (Table 3). It was found that in the elderly IgAN group that podocyte fusion remained an independent risk factor affecting prognosis after multiple factor adjustments (HR=5.72,*P*=0.011), while this was not observed in the young IgAN group. Therefore, it indicates that the degree of podocyte fusion has more significant clinical significance in influencing the prognosis of elderly patients with IgAN. Clarifying the causes of podocyte injury in the elderly is crucial for delaying the progression of IgAN.

High Expression of the cGAS-STING Pathway in Renal Sections of Patients with IgAN

In recent years, an increasing number of studies have found that senescence plays an important role in podocyte injury.[9] The cGAS-STING pathway is an important pathway for regulating cellular aging. We performed cGAS-STING staining on the renal pathological sections of patients and found that there was high expression of cGAS and pSTING in the renal tissues of IgAN patients, and co-localized with the podocyte marker Synaptopodin, indicating the existence of podocyte senescence induced by the activation of the cGAS-STING pathway in IgAN (Figure 4A). The degree of podocyte fusion was more severe in the pSTING positive group, and the expression of podocyte markers was lower than that in the negative group (Figure 4B).

We collected 90 cases of IgAN patients during the follow-up and performed pSTING immunofluorescence staining on their renal tissues. The results showed that among elderly patients aged 60 or above, there were 13 cases with positive pSTING, accounting for 86.7%, which was significantly higher than that of young patients (under 60 years old) (n=44, 58.7%) (Figure 5B). Further analysis revealed that the 24h UP and SCr levels of pSTING positive patients were

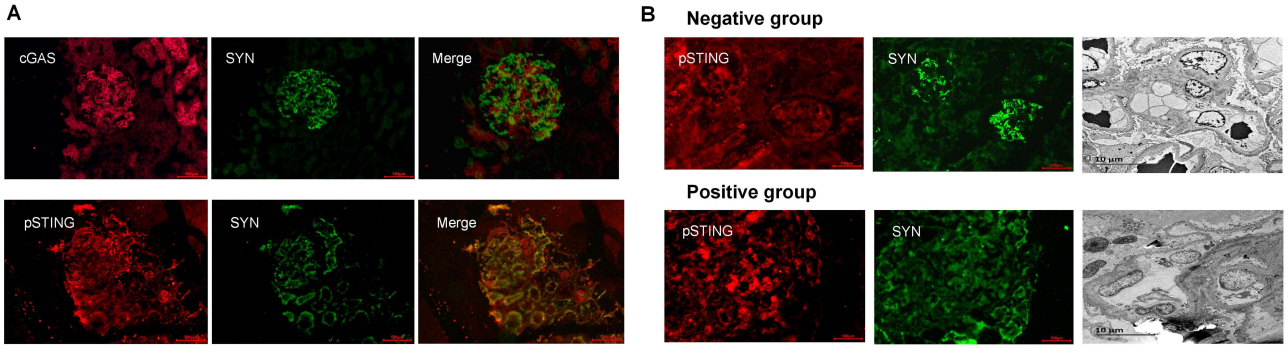

Figure 4 Immunofluorescence of cGAS-STING & the manifestations of the pSTING positive group and the pSTING negative group under electron microscopy and immunofluorescence. (**A**) cGAS /pSTING co-localized with the podocyte marker Synaptopodin; (**B**) The pSTING positive group exhibited more severe podocyte fusion under electron microscope and lower expression of Synaptopodin.

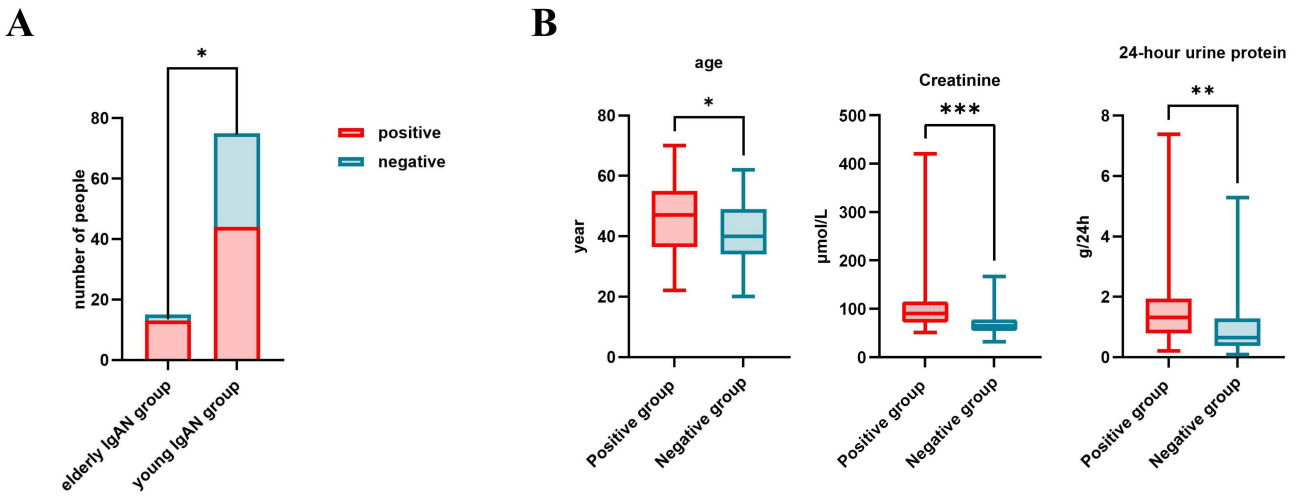

Figure 5 Clinical data of the pSTING positive group and the negative group. (**A**) compared the baseline characteristics (included age, SCr, 24h UP) between the pSTING immunofluorescence positive group and the negative group; (**B**) compared the proportion of pSTING immunofluorescence positivity in the elderly IgAN group and the young IgAN group. *Stands for P<0.05;**stands for P<0.01; ***stands for P<0.001.

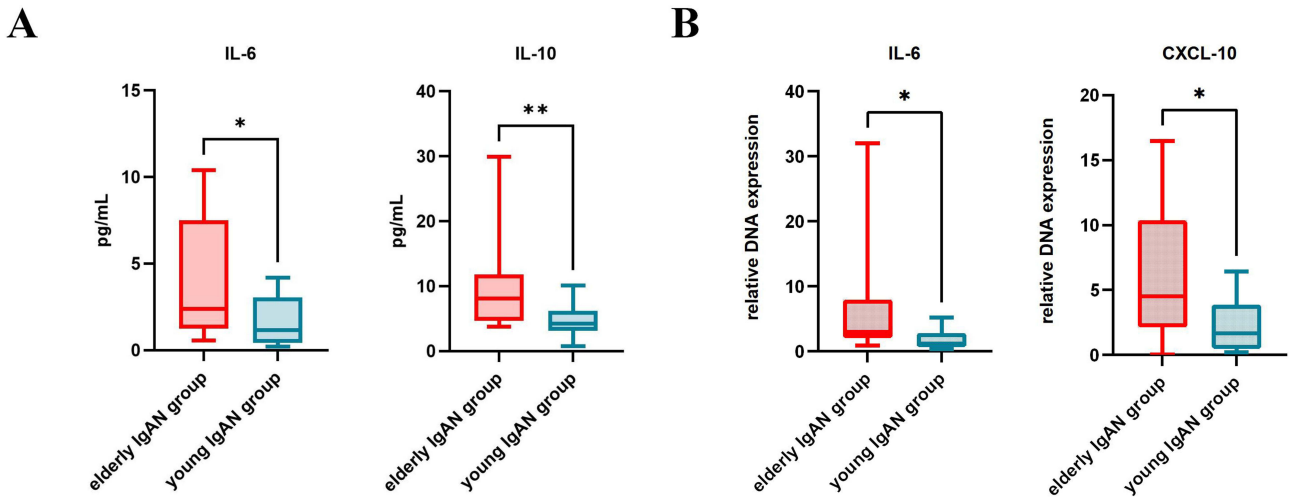

Figure 6 Comparison of SASP between the elderly IgAN group and the young IgAN group. (**A**) compared the SASP levels between the elderly IgAN group and the young IgAN group by ELISA. (**B**) compared the SASP levels between the elderly IgAN group and the young IgAN group by qPCR *Stands for P<0.05;**stands for P<0.01.

significantly higher than those of negative patients (Figure 5 A).The cGAS-STING pathway is a key upstream regulatory pathway for the activation of SASP. Therefore, we further detected common SASP in patients with IgAN. Through ELISA and PCR, we found that the levels of IL-10, IL-6 and CXCL-10 in the serum of patients in the pSTING positive group were significantly higher than those in the negative group (Figure 6A and B). It is indicated that in elderly patients, podocyte damage is mainly caused by aging, and the activation of the cGAS-STING pathway is an important pathway leading to senescence. Actively inhibiting the cGAS-STING pathway may become a new direction for the prevention and treatment of elderly patients with IgAN.

Discussion

IgAN is the most common primary glomerulonephritis worldwide.[10] Recurrent gross hematuria and proteinuria are the main clinical features of this disease. IgAN is common among young people. In the past, it was even regarded as a rare disease among the elderly. Since the 1990s, IgAN patients over 50 years old accounted for only 2.3% of all patients.[11] However, according to reports in 2009, this proportion increased to 18.3%.[12] In 2015, a study on IgAN in the elderly

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conducted by the Mayo Clinic found that approximately 22% of 207 IgAN patients were over 65 years old.[4] Meanwhile, a national survey in Japan in 2021 indicated that the incidence of IgAN among 2802 elderly patients (aged 65 and above) was 10.5%.[10] In our study, among the 1,012 IgAN patients we included, 119 were elderly people, accounting for 11.76%. Therefore, summarizing the characteristics and clinical features of the onset of IgAN in elderly patients and clarifying the pathogenesis of IgAN in the elderly are of vital importance for finding more suitable treatment plans for elderly patients and delaying the progression of the disease.

Previous studies have found that elderly patients with IgAN have a higher incidence of hypertension and arteriosclerosis, more severe tubulointerstitial fibrosis, higher urine protein quantification and a faster rate of eGFR decline. Overall, elderly patients exhibit more severe clinical symptoms and more complications.[4,13] In our study, we found similar results. Compared with young patients, the levels of proteinuria, creatinine and uric acid in elderly patients were significantly increased, while the levels of nutrition-related albumin and hemoglobin decreased. Comparative analysis of renal pathological features revealed a significantly elevated T1+2 score in elderly IgAN patients relative to the younger IgAN group. In contrast, assessment of immunofluorescence findings showed that the positive intensity for IgA was substantially lower in the elderly group. Therefore, we believe that renal pathology mainly characterized by chronic lesions dominates the onset of IgAN in the elderly, and the role of immune factors is not prominent. Further prognostic analysis revealed that the risk of renal endpoint events in elderly IgAN patients was 2.13 times that of young patients. Previous studies have also found similar conclusions. Although D 'Amia et al analyzed 17 factors related to the prognosis of IgAN and found that age was only a poor factor for the prognosis of IgAN in the univariate analysis.[4] Duan et al conducted a meta-analysis of nine related studies (including 6,543 patients), and pointed out that elderly IgAN patients progressed to ESRD 1.95 times more than non-elderly IgAN patients.[14] Meanwhile, Angel et al 's research found that the 2-year and 5-year survival rates of 151 elderly patients with IgAN during follow-up were 48% and 26%, respectively, which also suggests that the prognosis of elderly patients with IgAN is poorer.[15]

Previous studies have found that the podocyte hiatus membrane is the main factor maintaining the integrity of the glomerular filtration barrier. Podocyte fusion can cause the disappearance or reduction of the podocyte hiatus membrane, so podocyte injury can lead to the formation of proteinuria.[16] Our research suggests that the degree of podocyte fusion in elderly patients is more prominent than that in non-elderly patients. Notably, through KM analysis, we found that compared with patients with mild podocyte fusion, the incidence of endpoint events in patients with podocyte fusion of 50% or more is significantly higher, and this is more prominent in elderly patients. Even with similar levels of proteinuria, the proportion of elderly IgAN patients exhibiting podocyte fusion exceeding 50% remained significantly higher than that of young patients.This indicates that the impact of podocyte injury on prognosis increases with age. In recent years, an increasing number of studies have found that podocyte senescence is an important link and potential therapeutic target in renal injury.[17–19] In fact, in current models such as DN, FSGS, and AKI, cellular senescence has been confirmed to play a significant role in the disease process. Guo etal. 's research have revealed that renal tissues in diabetic nephropathy (DN) exhibit an elevated burden of senescent cells, with a predominant distribution observed in tubular epithelial cells and podocytes. The strategic clearance or targeted depletion of these senescent cells has emerged as a promising therapeutic avenue to decelerate the progression of DN.[20] Chen et al were found that administration of LXA4 inhibited the senescence of tubular epithelial cells and significantly restored the renal function of rats.[21] The research of Zhang et al shows that podocyte senescence induces glomerular sclerosis through AMPK-mTOR signaling.[18] It is worth noting that a study by Peking University pointed out that p16 INK 4A has the ability to arrest cells in the G1 phase of the cell cycle. Therefore, p16 INK 4A is regarded as a marker of cellular aging. Their research found that Although the upward trend of the percentage of p16 INK 4a positive cells in glomeruli and renal tubules in elderly patients was not statistically significant, the percentage of p16 INK 4a positive cell nuclei in renal interstitium was positively correlated with T score, while the increase in the percentage of p16 INK 4a positive cell nuclei in renal tubules was correlated with eGFR and 24h UP levels.[22] We also performed staining and localization of the senescence marker p16 on the renal tissues of patients with IgAN. The results showed that the senescence marker P16 was co-localized with podocytes.

The cGAS-STING pathway is a key pathway in innate immunity for identifying abnormal DNA in the cytoplasm. During the process of cellular senescence, nuclear DNA or mitochondrial DNA may leak into the cytoplasm due to

cellular damage, and these abnormal DNA will activate the cGAS-STING pathway. Once this pathway is activated, it will promote the SASP. In our study, we found that the cGAS-STING pathway protein was specifically expressed in podocytes, and it was significantly higher in elderly patients than in young patients. Further analysis revealed that patients with positive pSTING had higher levels of urine protein and serum creatinine, and their podocyte fusion was also more severe. Previous animal studies have also found the correlation between the cGAS-STING pathway and cellular senescence in dkd and aki. The research of Sherif et al has confirmed that the cGAS-STING pathway is an important contributor to the development of DKD and has clarified the sex dimodality of DKD.[23] LUO et al discovered that the cGAS inhibitor RU.521 could weaken the activation of NLRP3 inflammasome and S-AKI, which would be eliminated by the STING agonist DMXAA. Meanwhile, after inhibiting mtDNA replication with EtBr, the accumulation of cytoplasmic mtDNA and downregulation of cGAS-STING-NLRP3 axis could be reduced.[24]

The SASP which could be driven by the cGAS-STING pathway plays an important role in the aging process and related diseases. Wang et al conducted RNA-SEQ research on senescent podoccytes and discovered many aging-related genes, including 11 SASP genes. Research has found that inflammation-related genes and inflammasome pathways are significantly activated in senescent podocytes. Among them, the increased expression of Nfkb1 and Nfkb2 in senescent podocytes has been confirmed to be involved in renal aging.[25] In our research, we also discovered for the first time that the expression of SASP-related factors such as IL-10,IL-6, and CXCL-10 in the serum of elderly patients with IgAN was significantly higher than that of non-elderly patients. Further renal tissue staining revealed that in IgAN patients, senescent cells were mainly podocytes, and the degree of podocyte senescence in elderly patients was significantly higher than that in non-elderly patients. It can be inferred that in elderly patients with IgAN, podocyte senescence is an important cause that may lead to their damage and thereby affect the progression of kidney disease.

While this study provides valuable insights into the clinicopathological characteristics and prognostic factors of IgAN across different age groups, several limitations should be acknowledged. Firstly, the single-center, retrospective design may introduce selection bias. The study population was recruited from a single medical center, and the patient cohort may not fully represent the broader IgAN population, particularly in terms of regional differences in disease epidemiology, diagnostic criteria, or treatment strategies. Also, the definition of "elderly" and "young" groups (60 years as the cutoff) may be arbitrary. Although 60 years is a commonly used threshold for defining elderly populations in clinical research, the biological aging process varies individually, and this binary classification may overlook potential differences in disease characteristics or prognosis among patients near this cutoff (eg., those aged 55–65 years).Moreover,the assessment of podocyte fusion was based on electron microscopy, which may have inter-observer variability. While electron microscopy is the gold standard for evaluating podocyte morphology, the quantification of podocyte fusion relies on subjective judgment.

Also, incomplete data on disease duration from onset to renal biopsy precluded a precise evaluation of its impact on histologic changes, particularly podocyte injury. And although baseline use of ACEI/ARB/SGLT2 inhibitors was documented, medication adjustments during follow-up could not be fully accounted for, which may have affected podocyte injury.Besides, age-matched normal renal tissue controls were unavailable due to ethical and clinical constraints, limiting the distinction between renal-specific effects and systemic senescence. At last, the follow-up time may have been insufficient to capture long-term renal outcomes in some patients.The average follow-up time was 35.04 ±19.37 months, which may be too short to fully assess the progression to ESRD in a subset of patients, especially those with milder disease at baseline. Longer-term follow-up data would be needed to confirm the stability of the observed prognostic trends.

Conclusion

In conclusion, our study highlights age-related differences in IgAN and identifies key factors associated with prognosis. Elderly IgAN patients (≥60 years) exhibit distinct clinicopathological features, with chronic lesions and podocyte injury (severe fusion >50%) are closely linked to disease progression. Severe podocyte fusion emerges may serve as a independent prognostic factor specifically in the elderly IgAN group. Additionally, the cGAS-STING pathway is highly expressed in IgAN renal tissues, particularly in elderly patients, and its activation correlates with podocyte injury,

implying a potential association with age-related podocyte senescence.Targeting inhibition of cGAS-STING pathway to slow down podocyte senescence may become a new direction for prevention and treatment of IgAN in the elderly.

Targeted inhibition of the cGAS-STING pathway to attenuate podocyte senescence represents a promising preventive and therapeutic strategy for elderly IgAN patients.However, large-sample and long-term prospective studies are expected to be verify the independent prognostic value of severe podocyte fusion in elderly patients with IgAN. Additional research is also needed to further clarify the specific molecular mechanisms by which the cGAS-STING pathway contributes to age-related podocyte senescence and injury, including its interactions with the SASP and other aging-related signaling pathways.

Data Sharing Statement

The original contributions presented in the study are included in the Supplementary Material. Further inquiries can be directed to the corresponding author Xue Jiang.

Ethics Statement

Ethical approval for this study involving human subjects was obtained from the Ethics Committee of Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University (Reference Number: 2024KLL230). The study was conducted in accordance with the local legislation and the institutional requirements. A waiver of the requirement for written informed consent was granted for all participants, consistent with the provisions in the national guidelines for minimal risk research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

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