ORIGINAL ARTICLE

Immunoglobulin A Nephropathy: A 10-year Analysis in a Single Malaysian Centre

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ABSTRACT

Introduction: Immunoglobulin A nephropathy (IgAN), also referred to as Berger's disease, is the leading primary glomerular disease cause of end-stage kidney disease (ESKD). Its prevalence, presentation, and progression have been shown to vary between different regions and ethnicities. This study aims to explore the presentation, predictors of disease progression, and outcome in a cohort of Malaysian patients with IgAN. **Methods:** This study evaluated retrospective data from 82 patients with renal biopsy-proven IgAN. The patients were classified into two categories based on their estimated glomerular filtration rate (eGFR) at the last follow-up: those with progressive disease (50% reduction in eGFR from the time of biopsy and/or eGFR <15 ml/min/1.73 m^2) and those with non-progressive disease. **Results:** The majority of patients (75.6%) were female and, 47.6% were less than 30 years old at the time of the renal biopsy. The most common clinical presentation was proteinuria (86.4%). At the end of a median follow-up of 2.7 (IQR 1.2-5.1) years, 29.3% of patients reached the combined renal outcome. Males were more likely than females to have progressive disease (OR = 2.89). The survival rates without ESKD at five and ten years are 82% and 78%, respectively. Multivariate cox regression analysis showed MAP (HR =1.05 95% CI 1.01-1.10), UPCI (HR=13.67 95%CI 1.06-175.88), and MESTC score >3 (HR=3.95 95%CI 1.09-14.23) as predictors of the combined renal outcome. **Conclusion:** IgAN is not a benign disease, with a significant progression to ESKD in this cohort. MAP, UPCI, and MESTC >3 are predictors of disease progression.
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Keywords: IgA nephropathy; End stage kidney disease; Glomerulonephritis; Disease progression; Berger's disease

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INTRODUCTION

IgA nephropathy (IgAN) is a primary cause of glomerulonephritis worldwide (1). It is typically diagnosed through renal biopsy, which involves identifying predominant IgA staining in the mesangium during an immunofluorescence study (2). The exact cause of IgA nephropathy is not fully understood, but it is believed to involve a combination of genetic predisposition (3,4) immune dysregulation (5), and environmental triggers (6,7). Multihit theory of the involved pathogenetic process has been proposed (8). Repeated Toll-like receptor 9 (TLR9) activation from mucosal infections in the presence of genetic susceptibility induces tonsillar expression of B-cell activating factor (BAFF), causing B-cell expansion and a proliferation-inducing ligand (APRIL), which promotes the generation of plasma cells producing antibodies. The plasma cells produce increased amounts of polymeric IgA1, a subtype of IgA, in the mucosal areas, particularly the respiratory and gastrointestinal tracts. This abnormal IgA1 has an aberrant glycosylation pattern (galactose deficient IgA1) and are recognised as autoantigens (hit 1). Antibodies, usually IgG and IgA, are then formed against these autoantigens (hit 2) with a resultant immune complex formation (hit 3). The immune complexes containing abnormal IgA1 are deposited in the mesangial region of the glomeruli (hit 4). This deposition triggers an inflammatory response. The deposited immune complexes activate the complement system and attract immune cells, such as neutrophils and macrophages, to the glomerular area. These cells release pro-inflammatory molecules, leading to further

tissue damage. Prolonged and repetitive inflammation in the glomeruli results in glomerular injury and fibrosis (8).

The prevalence of IgAN varies across different regions, with the highest incidence found in Asia and the lowest in people of African descent (9). According to the 2020 Malaysian Registry of Renal Biopsy report, the prevalence of IgAN in Malaysia increased steadily from 19.6% of primary glomerular diseases in the year 2005 to 29.5% in the year 2020 (10).

The clinical presentation of IgAN is diverse and varies by region. IgAN is the leading primary glomerular disease that can lead to chronic kidney disease (11). In fact, an estimated 40% of patients with IgAN deteriorate to end-stage kidney disease (ESKD) within 20 years of a renal biopsy (12). Thus, it is crucial to predict the risk of disease progression early on, as this enables the institution of drug therapy to delay ESKD. Moreover, it helps prevent the exposure of patients with a low risk of disease progression to the side effects of immunosuppression used to treat progressive disease.

Several clinical markers, such as proteinuria >1 g/day, reduced estimated glomerular filtration rate (eGFR), and the Oxford histologic classification, have been shown to have varying predictive values in patients with IgAN (13). Notably, the Oxford histologic classification has been shown to predict disease progression earlier than 2-year clinical data (14). This study aims to determine the presentation and outcome of IgAN and the clinical utility of these markers in our cohort.

MATERIALS AND METHODS

Patients Selection

Retrospective data on patients with biopsy-proven IgAN diagnosed between 2012 and 2022 at Hospital Serdang, Malaysia, was collected. Patients who had a pre-existing systemic disease that can involve the kidneys, such as diabetes, systemic lupus erythematosus, psoriasis, etc., patients who had ESKD at the time of histologic diagnosis, patients younger than 18 years old; those who had a renal transplant before biopsy; those with less than 8 glomeruli seen on light microscopy; and those who had less than 6 months of follow up after renal biopsy were excluded (Table I). The research was conducted in accordance with the Declaration of Helsinki after approval by the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (NMRR ID-22-01020-ZFU (IIR) and the clinical research centre of Hospital Serdang.

Table I : Patients selection criteria

Criteria	Frequency
Inclusion criteria	
All biopsy-proven IgA nephropathy patients diagnosed between 2012 and 2022 at Hospital Serdang, Malaysia	184
Exclusion criteria	
Baseline data not available	33
End stage kidney disease at the time of kidney biopsy	23
Pre-existing diabetes, systemic lupus erythematosus, psoriasis, etc.	20
Less than 6 months of follow up after renal biopsy	9
Age less than 18 years old	5
History of renal transplant prior to kidney biopsy	5
Less than 8 glomeruli seen on light microscopy	5
Repeat kidney biopsy.	2
Patients included	82

Data Collection

Retrospective Patients' clinical and pathological data were extracted from the hospital's database. Information such as demographics, clinical, and laboratory data at the time of renal biopsy, including age, gender, blood pressure, serum protein, albumin, cholesterol, uric acid, 24-hour urine protein, urine protein creatinine index (UPCI), and serum creatinine, was extracted. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-2021) equation. Mean arterial blood pressure (MAP) was defined as the sum of diastolic blood pressure and one-third of the pulse pressure. All renal biopsy specimens were assessed according to the Oxford classification. The Oxford classification data include mesangial hypercellularity occurring in greater than 50% scored as M1, while < 50% is scored M0; absent endocapillary hypercellularity is scored E0 and E1 if present; absent segmental glomerulosclerosis is scored S0 and S1 if present; tubular atrophy/interstitial fibrosis is scored T0 if less than 25%, T1 if between 25% and 50% and T2 if more than 50%; and cellular/fibro cellular crescents were scored C0 if absent, C1 if present in less than 25%, or C2 if present in greater than 25% of glomeruli (MEST-C). The sum of the individual component of the MEST-C was the MEST-C score. Renin-angiotensin system blockade refers to the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) or both before or at biopsy.

Study outcome

The primary research outcome was defined as a 50% reduction in eGFR from the time of biopsy during follow-up, or ESKD (eGFR < 15 ml/min per 1.73 m^2).

Data Analysis

Normally distributed numerical variables were expressed as mean (SD), while median (interquartile range, IQR) was used for variables not normally distributed. Independent students' t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test was used to compare non-normally distributed variables. Categorical variables were expressed as frequencies and percentages and analysed using the chi-square test. Cox regression analysis was used to determine the predictors for progression to ESKD or 50% reduction in eGFR and was expressed as hazard ratios with a 95% confidence interval. IBM SPSS version 28 was used to analyse the data. P-values were 2-tailed and considered statistically significant if <0.05.

RESULTS

Table II shows the baseline characteristics of patients at the time of the kidney biopsy. The mean (SD) age at the time of biopsy was 33.5 (10.7) years; 62 patients were female, with a male-to-female ratio of 1:3. Malays were the largest racial group (78.0%). The median (IQR) 24-hour proteinuria was 2.7 (1.5 – 5.0) g/day, the mean (SD) serum creatinine was 124.9 (81.2) µmol/L, mean (SD) eGFR was 75.8 (36.9) ml/min per 1.73 m2, and the uric acid was 452.8 (129.6) µmol/L. Proteinuria was the commonest presentation (86.4%). At biopsy, 41.5% of patients were hypertensive. According to the Oxford classification, 72 (87.8%), 17 (20.7%), 73 (89.0%), 40 (48.8%), and 33 (41.3%) patients had M1, E1, S1, T1-2, and C1-2 lesions in their renal

Table II : Sociodemographic and Baseline Characteristics of IgAN Patients at the Time of Renal Biopsy

Characteristics	Frequency (%)	Mean + SD or Median (IQR)
n	82	
Age at biopsy (years)		33.5 ± 10.7
< 30	38 (47.6)	
31 – 40	22 (26.8)	
41 – 50	15 (18.3)	
51 – 60	4 (4.9)	
> 60	2 (2.4)	
Gender		
Male	20 (24.4)	
Female	62 (75.6)	
Race		
Malay	64 (78.0)	
Chinese	6 (7.3)	
Indians	6 (7.3)	
Others	6 (7.3)	
Clinical presentation		
Proteinuria	70 (86.4)	
Haematuria	54 (65.9)	
AKI	4 (4.9)	
Hypertension	34 (41.5)	
Blood Pressure		
SBP (mmHg)		133.7 ± 20.1
DBP (mmHg)		82.6 ± 14.3
MAP (mmHg)		97.5 ± 15.3
Creatinine (µmol/L)		124.9 ± 81.2
eGFR (ml/min/1.73m^2)		75.8 ± 36.9
CKD Stage		
I	33 (40.2)	
II	19 (23.2)	
III	16 (19.5)	
IV	14 (17.1)	
Cholesterol (mg/L)		6.6 ± 2.2

Haematocrit (g/dl)	12.3 ± 1.4
Uric acid (μmol/L)	452.8 ± 129.6
Protein (g/L)	65.6 ± 8.4
Albumin (g/L)	30.1 ± 7.0
24-HRUP (g/day)	2.7 (1.5 – 5.0)
UPCI	0.39 ± 0.27
< 0.03 g/mmol	1 (1.2)
0.03 - 0.3 g/mmol	36 (44.4)
> 0.3 g/mmol	43 (53.1)
Histology	
M1	72 (87.8)
E1	17 (20.7)
S1	73 (89.0)
TI-2	40 (48.8)
C1-2	33 (41.3)
MEST-C>3	24 (29.3)
Treatment	
ACEI/ARB	62 (75.6)
Corticosteroid	22 (26.8)
Cyclosporine/MMF/Cyclophosphamide	3(3.7)

Others: people of other minority ethnic groups e.g., Iban, kadazan, AKI: acute kidney injury, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, eGFR: estimated glomerular filtration rate, CKD: chronic kidney disease, 24HRUP: 24-hour urinary protein, UPCI: urine protein creatinine index, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, MMF: mycophenolate mofetil.

biopsy specimens, respectively. Twenty-four (29.3%) patients had a MEST-C score > 3. About 75.6% of patients were commenced on ACEI/ARB in line with the kidney disease: improving global outcome (KDIGO) guideline. At the end of a median (IQR) follow-up of 2.7 (1.2 - 5.1) years, 24 (29.3%) patients reached the study composite outcome; 10 (12.2%) had a 50% decline in eGFR from the time of biopsy, while 14 (17.1%) had ESKD. Half of the incidence of ESKD occurred within the first year of renal biopsy. Although there were more females in the study, males were more likely to have progressive disease (odds ratio 2.89) (Fig. 1).

Patients were also compared for the progress of the diseases, i.e., those with progressive and non-progressive diseases using baseline characteristics (Table III). Renal function at the time of biopsy was significantly reduced in patients with progressive disease, as evidenced by elevated serum creatinine and reduced eGFR (both P < 0.001). The mean (SD) of age, 24-hour proteinuria, haemoglobin concentration, cholesterol, and albumin showed no statistical difference between the groups. Meanwhile, T1-2 and C1-2 lesions were significantly higher (79.2% vs. 36.2%) and (54.1% vs. 34.5%), respectively, in patients with progressive and non-progressive diseases. It was found that MEST-C scores >3 occurred significantly more frequently among patients with progressive disease (p = 0.02).

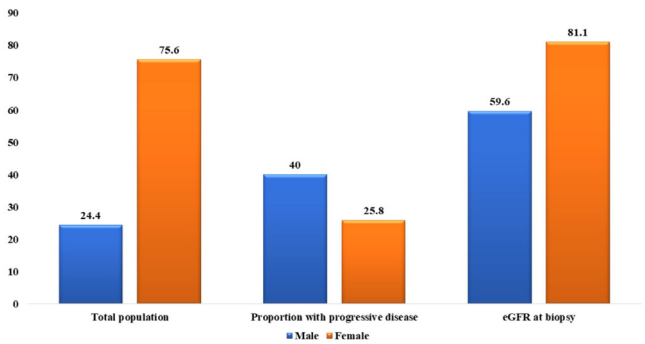

Fig. 1 : Comparison of IgAN by gender.

On survival analysis (Table IV), univariate cox regression analysis showed MAP (HR =1.03 95% CI 1.01-1.05), eGFR (HR =0.959 95% CI 0.9418 - 0.978), serum creatinine (HR =1.013 95% CI 1.008 - 1.018), uric acid (HR = 1.01 95% CI 1.00-1.01), UPCI (HR =5.478 95% CI 1.173-25.594), and MEST-C score >3 (HR =0.460 95% CI 0.099 – 2.149). Detailed further multivariate analysis found MAP (HR =1.05 95% CI 1.01-1.10), UPCI (HR =13.67 95% CI 1.06-175.88), and MESTC score >3 (HR =3.95 95% CI 1.09-14.23) as predictors of the primary renal outcome. Kaplan Meier's survival analysis (Fig. 2) showed cumulative renal survival without ESRD or a 50% decline in eGFR of 68.5% and 40.8% at five and ten years, respectively. The log-rank test showed significant differences in renal survival classified based on UPCI, the T-score, and MEST-C score.

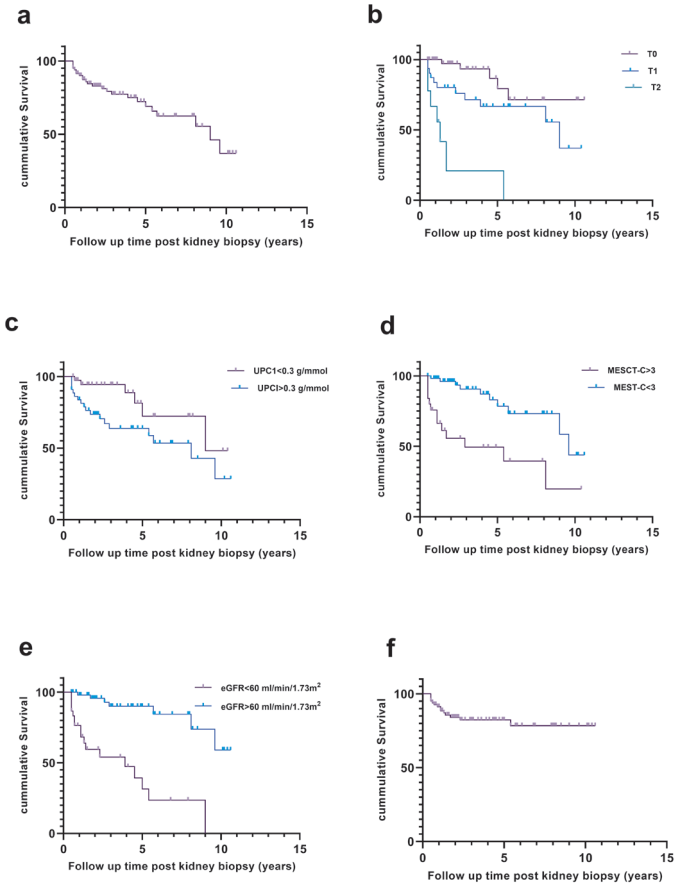

Fig. 2 : Kaplan-Meier curves showing survival without the composite primary renal outcome (50% reduction of eGFR or ESKD) from the time of biopsy a) in the entire cohort categorized by; b) tubular atrophy and interstitial fibrosis, T-score, c) urinary protein creatinine index, UPCI and d) MEST-C Score >3, e) eGFR. Fig. 2f depicts Kaplan-Meier curve showing survival without ESKD from the time of biopsy to last follow-up.

This study also documented that at the last follow-up (Table V), about 15.9% of patients had UPCI <0.03 g/mmol, while 51.2% had partial remission of proteinuria between 0.03 and 0.3g/mmol. Blood pressure control was achieved with BP < 130/80 mmHg in 46.3% of patients. Cases of complications from therapy such as steroid-induced diabetes were observed in 11.8% of patients who had steroid therapy.

DISCUSSION

Immunoglobulin A nephropathy accounts for the largest primary glomerular disease around the world, reaching over 40% of primary glomerular disease in Singapore and China (9). It accounts for 24.5% in Malaysia (10). The presentation and outcome have been shown to vary between different regions and ethnicities. The mean (SD) age at the time of the renal biopsy was 33.5 (10.7) years. Almost half of the patients were diagnosed before the age of 30, and more than three-quarters were diagnosed before they were 40 years old. The age profile of the patients in this study is similar to those reported in other populations around the world (15). It is not exactly clear why IgAN is commoner in young people. Possible reasons include the fact that autoimmune diseases are commoner among young people (16), younger individuals often have higher exposure rates to environmental factors, such as infections and certain allergens, which may play a role in triggering or exacerbating IgA nephropathy. This is exemplified by the occurrence of synpharyngitic haematuria (gross haematuria during episodes of pharyngitis) presentation reported in young people (17).

The patients were predominantly female, accounting for about 2/3 of the patients. This is in keeping with reports from other parts of Malaysia and the national reports of the Malaysian Renal Biopsy Registry (10,18,19). It is in contrast to the male preponderance reported among Caucasians and East Asians (20,21). This could be due to differences in pathogenetic mechanisms but this requires further research. It may also be attributed to the routine urine screening at the antenatal unit with subsequent referrals to the nephrologist considering that most of the women were of childbearing age. In this regard, it may be a case of increase detection as against increase prevalence. A similar scenario was reported from another Malaysian centre (18). Malaysia is a multiracial country consisting of Malays, Chinese, Indians and other minor ethnicities. Most (78%) of the IgAN patients in this study are Malays. Chinese, Indians and other minor ethnicities made up 7.3% of patients each. The preponderance of the Malays can be explained by the demographics of the population around the location of our centre, as they constituted 65.6% of patients seen in the centre in the study period. This, however, represents a drift from the almost uniform racial distribution reported in studies conducted three decades earlier (22,23).

Like elsewhere, the most common presentations were urine abnormalities of proteinuria (86.4%) and haematuria (65.9%). The median (IQR) 24-hour proteinuria was 2.7 (1.54-5.05) g/day. This is similar to another Malaysian report (18) but is higher than the reported proteinuria in other ethnicities (24). Correspondingly, UPCI >0.3 g/mmol at the time of biopsy was observed in more than half of the patients. These may be explained by the renal biopsy schedule in this centre, in which biopsy is undertaken when the proteinuria persists at more than 1g per day. It may also be related to the fact that, at the time of biopsy, renal function determined by eGFR is lower in our patients compared to other ethnicities (25). Using the Oxford classification of renal biopsy on light microscopy, there was a high proportion of segmental sclerosis, tubular atrophy/interstitial fibrosis among the patients. This may be due to a late patient presentation. It may also be due to differences in the genetics or underlying pathogenesis of the disease in our cohort.

Table III : Comparison of Clinical, Histological and Laboratory Characteristics of Patients with Progressive and Non-Progressive Disease at The Time of Renal Biopsy

Characteristics	Progressive Disease	Non-progressive Disease	p-value
n	24 (29.3%)	58 (70.7%)	
Age at biopsy (years)	32.29 ± 10.32	33.93 ± 10.9	0.533
Gender			
Male	8 (40.0%)	12 (60.0%)	0.225
Female	16 (25.8%)	46 (74.2%)	
Race			
Malay	21 (32.8%)	43 (67.2%)	0.281
Chinese	1 (16.7%)	5 (83.3%)	
Indians	0 (0%)	6 (100%)	
Others	1 (16.7%)	5 (83.3%)	
MAP (mmHg)	107.72 ± 13.04	96.24 ± 14.52	0.001*
Creatinine (µmol/L)	184.33 ± 88.64	100.33 ± 64.15	<0.001*
eGFR (ml/min/1.73m^2)	46.79 ± 26.05	87.88 ± 34.06	<0.001*
Cholesterol (mg/dL)	6.63 ± 2.34	6.62 ± 2.22	0.999
Haemoglobin (g/dL)	11.92 ± 1.42	12.46 ± 1.39	0.329
Uric acid (µmol/L)	497.13 ± 108.21	425.40 ± 115.22	0.040*
Protein (g/dL)	65.98 ± 9.31	63.80 ± 9.44	0.386
Albumin (g/dL)	30.67 ± 6.13	30.31 ± 7.90	0.844
24-HRUP (g/day)	4.3 (3.5)	2.6 (3.2)	0.164
UPCI (g/mmol)	0.48 ± 0.25	0.34 ± 0.24	0.018*
Histology			
M1	21 (87.5%)	51 (87.7%)	0.957
E1	6 (25.0%)	11 (19.0%)	0.540
S1	20 (91.7%)	53 (87.9%)	0.622
T1-2	19 (79.2%)	21 (36.2%)	<0.001*
C1-2	13 (54.1%)	20 (34.5%)	0.141
MEST-C >3	18 (85.7%)	37 (62.7%)	<0.001*

MAP: mean arterial pressure, eGFR: estimated glomerular filtration rate, 24HRUP: 24-hour urinary protein, UPCI: urine protein creatinine index, M: Mesangial hypercellularity, E: **E**ndocapillary proliferation, S: **S**egmental glomerulosclerosis, T: **T**ubular or interstitial fibrosis, C: crescent formation, MEST-C>3: cumulative MEST-C Score >3

At the last follow-up, 17.1% of patients had ESKD. It was noted that even though there were more females with IgAN, the proportion of males who developed ESKD was higher, and men had a lower eGFR at the time of biopsy (Fig. 1). At the time of biopsy, eGFR, serum creatinine, uric acid, UPCI, mean arterial pressure, and the presence of tubular atrophy or interstitial fibrosis were predictive of the renal outcome on univariate analysis. On multivariate analysis, mean arterial pressure, UPCI, and MEST-C >3 remained. Several studies have shown the different components of the Oxford classifications to be predictive of the renal outcome; the most consistent has been the T score (2), while others reported none, similar to our study (26).

Kaplan-Meier's survival analysis (Fig. 2a) revealed cumulative renal survival without ESRD or >50% decline in eGFR of 68.5% and 40.8% at five and ten years, respectively. Survival without ESKD (Fig. 2f) was higher: 82% at five years and 78% at ten years. This is lower than reports from the Japanese and Chinese (26,27) but higher than renal survival among Indians (28). The logrank test showed significant differences in renal survival classified based on UPCI ($p = 0.02$), the T-score ($P < 0.001$) and MEST-C score >3 ($P<0.001$)

This study is limited by its retrospective design with a short follow-up period and its relatively small sample size. The outcome measures may be affected by other confounding factors that cannot be accounted for such as drug compliance and effect/adverse effects of medications prescribed or otherwise.

Table IV : Correlation between the clinical, histological and laboratory characteristics at the time of biopsy and the primary renal outcomes

	95% Confidence Interval			
	HR	**LOWER**	**UPPER**	**P-VALUE**
Univariate Cox Regression				
Age at biopsy (years)	1.00	0.96	1.04	0.889
Female	1.85	0.76	4.34	0.160
MAP	1.03	1.01	1.05	0.005*
BMI	1.02	0.95	1.01	0.663
Creatinine	1.02	1.01	1.02	<0.001*
eGFR	0.96	0.94	0.98	<0.001*
Cholesterol	0.97	0.79	1.19	0.777
Haemoglobin	1.05	0.97	1.12	0.245
Uric acid	1.01	1.00	1.01	0.012*
Serum protein	0.98	0.93	1.03	0.353
Serum albumin	1.01	0.95	1.07	0.814
24-HRUP	1.08	0.94	1.24	0.291
UPCI	7.20	1.75	29.69	0.006*
M1	0.95	0.28	3.27	0.933
E1	1.33	0.52	3.37	0.551
S1	1.27	0.30	5.45	0.745
T1-2	3.88	2.09	7.22	<0.001*
C1-2	2.13	0.95	4.79	0.068
MEST-C >3	4.03	1.80	9.02	<0.001*
Multivariate Cox Regression				
MAP	1.05	1.01	1.10	0.016*
Creatinine	1.01	0.99	1.02	0.254
eGFR	1.00	0.97	1.05	0.831
Uric acid	1.01	1.00	1.01	0.229
UPCI	13.67	1.06	175.88	0.045*
T1-2	2.65	0.57	12.40	0.216
MEST-C >3	3.95	1.10	14.24	0.036*

MAP: mean arterial pressure, eGFR: estimated glomerular filtration rate, 24HRUP: 24-hour urinary protein, UPCI: urine protein creatinine index, M: Mesangial hypercellularity, E: **E**ndocapillary proliferation, S: **S**egmental glomerulosclerosis, T: **T**ubular or interstitial fibrosis, C: crescent formation, MEST-C>3: cumulative MEST-C Score >3

Table V : Patients' characteristics as at last follow-up

	Frequency (%)
UPCI (g/mmol)	
<0.03	15.9
0.03-0.3	51.2
>0.3	32.9
Blood pressure ≤130/80 mmHg	46.3
Steroid induced DM	11.8

UPCI: urinary protein creatinine index, DM: diabetes mellitus.

CONCLUSION

There is a female preponderance of IgAN in our cohort. IgAN in this cohort is not benign, as the proportion of disease progression to ESKD was quite notable. Attention to male patients, and those with tubular atrophy/interstitial fibrosis: control of blood pressure and proteinuria would be beneficial to delay disease progression.

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