

Clinicopathological Spectrum of IgA Nephropathy in Erbil Teaching Hospital. A Retrospective Single Center Study

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ABSTRACT:

BACKGROUND:

The leading cause of glomerulonephritis that occurs most frequently and has the greatest morbidity and mortality rates worldwide are Immunoglobulin A nephropathy (IgAN). Internationally, the prevalence and clinicopathological range of primary Immunoglobulin A nephropathy (IgAN) is diverse.

AIMS:

This study aims to assess the clinical, pathological, and laboratory characteristics of male and female IgAN patients.

METHODS:

This is a retrospective Single center study, conducted in Erbil teaching hospital. All Native biopsy reports from 2015 to 2021 were reviewed and those with the diagnosis of IgA nephropathy were selected and their pathological, clinical, and laboratory data were analyzed and categorized using the Oxford categorization method.

RESULTS:

Out of 2649 biopsies done from 2015 to 2021 167. had IgA nephropathy, hence prevalence is 6.3%. Mean age was 34.03, Males comprised (67.1%), Females (32.9%). (68.3%) of patients had hypertension, (49.7%) of the patients had renal impairment, 38% had microscopic hematuria, and 19.8% had macroscopic haematuria. More than half (56.3%) of the males had renal impairment, compared with 36.4% of females ($p = 0.016$)

CONCLUSION:

Ig A nephropathy is common with variable presentations. Males have worse clinical and pathological features. High BMI is associated with higher blood pressure and more proteinuria. Larger studies are required to confirm, these findings.

KEYWORDS: glomerulonephritis, Immunoglobulin A nephropathy, renal impairment.

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INTRODUCTION:

IgAN is the most common biopsy-proven glomerular disease worldwide⁽¹⁾. It was first described by Berger and Hinglais in 1968⁽²⁾. It is an Immune complex-mediated disease usually defined by the presence of dominant IgA deposits in the glomerular mesangium⁽³⁾. The etiology is multifactorial with genetic, environmental, and genetic factors playing role in its incidence.^(4,5) It has a variable clinical course, ranging from isolated microscopic hematuria to rapidly progressive leading to renal failure. Initially, it was

described as a benign disease⁽²⁾ but more recent studies with longer follow-up time showed that the prognosis is poor with up to 30-40% of patients developing end-stage kidney disease within 10 to 25 years.⁽⁶⁾ Histological features are also variables ranging from mild mesangial hypercellularity to concentric glomerulonephritis and diffuse sclerosis^(6,7) Oxford classification was published in 2009 as a useful tool to assess prognosis depending on pathological variables and independent of clinical data. It is a necessary part

IGA NEPHROPATHY IN ERBIL

of a pathological report.⁽⁸⁾ In 2016 a study stated that MEST score combined with clinical data has the same prognostic ability to monitor clinical data for 2 years.⁽⁹⁾ There is still no approved therapy for IgA nephropathy⁽¹⁰⁾.

In 2019 an international risk prediction tool was validated to assess disease progression and patient risk stratification that uses readily available clinical and histological data.⁽¹⁰⁾ In the light of diverse clinical presentation and diverse pathological features of the disease, a more personalized treatment approach is warranted⁽¹¹⁾. Each patient's risk of disease progression can be computed online using the international risk prediction tool⁽¹¹⁾. This study aims to review cases of IgA nephropathy treated in our center over 7-year period, to assess the prevalence of the disease and analyze the clinical and pathological spectrum of the disease.

METHODS:

This is a retrospective study conducted in Erbil teaching hospital in Erbil /Kurdistan region in Iraq. We reviewed all the native biopsy reports performed from January 2015 to December 2021 and selected the biopsy reports of I IgA

nephropathy patients. We also obtained the clinical and laboratory data of those patients from hospital records.

All patients' data were fully anonymized before access and the study didn't include any human intervention thus informed consent was not required. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). The Chi-square test of association was used to compare the proportions of two or more groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. An unpaired t-test was used to compare two means, and one-way ANOVA was used to compare three or more means. A post hoc test (LSD) was used to compare every two means (after ANOVA). A p-value of ≤ 0.05 was considered statistically significant.

RESULTS:

The total number of patients who underwent renal biopsy during 2015-2021 was 2649 patients. IgA nephropathy was detected in 167 patients. Accordingly, the prevalence of IgA nephropathy was 6.3% (Figure1).

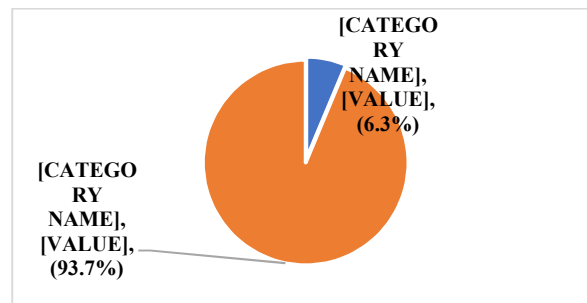


Figure1: Prevalence of IgA nephropathy.

The mean age (SD) of patients with IgA nephropathy was 34.03 (13.4) years, the median was 32 years, and the age range was 3-72 years. Half of the patients were in the age group 20-29

years (24%) and 30-39 years (26.9%), and more than two-thirds (67.1%) were males. More than half (55.1%) of the patients were smokers (Table 1).

Table 1: Basic characteristics.

	No.	(%)
Age (years)		
< 10	1	(0.6)
10-19	24	(14.4)
20-29	40	(24.0)
30-39	45	(26.9)
40-49	34	(20.4)
50-59	16	(9.6)
≥ 60	7	(4.2)
Gender		
Male	112	(67.1)
Female	55	(32.9)
Smoking		
Yes	92	(55.1)
No	75	(44.9)
Total	167	(100.0)

More than two-thirds (68.3%) of patients (with IgA nephropathy) had hypertension, 51.5% had edema, 38% had microscopic hematuria, and 19.8% had macroscopic hematuria. Regarding proteinuria, only 13.2% of the patients had no proteinuria.

Around half (49.7%) of the patients had renal impairment, 5.4% had a family history of renal disease, and the majority (86.8%) had no associated comorbidities (Table 2).

Table 2: Clinical characteristics and medical history.

	No.	(%)
Hypertension		
Yes	114	(68.3)
No	53	(31.7)
Edema		
Yes	86	(51.5)
No	81	(48.5)
Hematuria		
Micro	64	(38.3)
Macro	33	(19.8)
None	70	(41.9)
Proteinuria		
Non-nephrotic	128	(76.6)
Nephrotic	17	(10.2)
None	22	(13.2)
Renal impairment		
Yes	83	(49.7)
No	84	(50.3)
Family history of renal disease		
Yes	9	(5.4)
No	158	(94.6)
Comorbidities		
Respiratory	8	(4.8)
GIT	5	(3.0)
Others	9	(5.4)
None	145	(86.8)
Total	167	(100.0)

More than half (56.3%) of the males had renal impairment, compared with 36.4% of females ($p = 0.016$). The prevalence of renal impairment was 58% among patients with M0, and 29.2% among patients with M1 ($p = 0.001$). No significant association was detected between endocapillary hypercellularity (E) with renal impairment ($p = 0.693$). The prevalence of renal impairment

was significantly ($p = 0.003$) higher among patients with S1 (57.4%) than in patients with S0 (32.7%). The more the degree of tubular atrophy (T), the more the prevalence of renal impairment ($p < 0.001$). The prevalence among patients with C1 (64.5%) was higher than that among C0 (46.3%), but the difference was close to the level of significance ($p = 0.068$) (Table 3).

Table 3: Renal impairment by gender and MEST-C score.

	Renal impairment		Total	p
	Yes	No		
	No. (%)	No. (%)	No. (%)	
Gender				
Male	63 (56.3)	49 (43.8)	112 (100.0)	
Female	20 (36.4)	35 (63.6)	55 (100.0)	0.016*
M				
0	69 (58.0)	50 (42.0)	119 (100.0)	
1	14 (29.2)	34 (70.8)	48 (100.0)	0.001*
E				
0	59 (48.8)	62 (51.2)	121 (100.0)	
1	24 (52.2)	22 (47.8)	46 (100.0)	0.693*
S				
0	17 (32.7)	35 (67.3)	52 (100.0)	
1	66 (57.4)	49 (42.6)	115 (100.0)	0.003*
T				
0	24 (25.0)	72 (75.0)	96 (100.0)	
1	35 (79.5)	9 (20.5)	44 (100.0)	
2	24 (88.9)	3 (11.1)	27 (100.0)	<0.001*
C				
0	63 (46.3)	73 (53.7)	136 (100.0)	
1	20 (64.5)	11 (35.5)	31 (100.0)	0.068*
Total	83 (49.7)	84 (50.3)	167 (100.0)	

*By Chi square test.

No significant association was detected between gender and hematuria ($p = 0.214$). The prevalence of microscopic hematuria was 43.8% among M1 patients, compared with 36.1% among M0 patients. No significant association was detected between endocapillary hypercellularity (E), segmental glomerulosclerosis (S) with hematuria ($p = 0.308$,

and $p = 0.351$ respectively). Regarding tubular atrophy, the more the degree of atrophy, the less the rates of micro and macroscopic hematuria ($p < 0.001$). No significant association was detected between cellular crescent (C) with hematuria ($p = 0.525$) (Table 4).

Table 4: Hematuria by gender and MEST-C score.

	Hematuria				
	Micro	Macro	None	Total	P value
	No. (%)	No. (%)	No. (%)	No. (%)	
Gender					
Male	46 (41.1)	18 (16.1)	48 (42.9)	112 (100.0)	
Female	18 (32.7)	15 (27.3)	22 (40.0)	55 (100.0)	0.214*
M					
0	43 (36.1)	19 (16.0)	57 (47.9)	119 (100.0)	
1	21 (43.8)	14 (29.2)	13 (27.1)	48 (100.0)	0.029*
E					
0	50 (41.3)	21 (17.4)	50 (41.3)	121 (100.0)	
1	14 (30.4)	12 (26.1)	20 (43.5)	46 (100.0)	0.308*
S					
0	21 (40.4)	13 (25.0)	18 (34.6)	52 (100.0)	
1	43 (37.4)	20 (17.4)	52 (45.2)	115 (100.0)	0.351*
T					
0	42 (43.8)	28 (29.2)	26 (27.1)	96 (100.0)	
1	16 (36.4)	4 (9.1)	24 (54.5)	44 (100.0)	
2	6 (22.2)	1 (3.7)	20 (74.1)	27 (100.0)	<0.001*
C					
0	52 (38.2)	29 (21.3)	55 (40.4)	136 (100.0)	
1	12 (38.7)	4 (12.9)	15 (48.4)	31 (100.0)	0.525*
Total	64 (38.3)	33 (19.8)	70 (41.9)	167 (100.0)	

*By Chi square test.

No significant association was detected between the rate of proteinuria and the following variables: gender (p = 0.824), mesangial hypercellularity (p = 0.289), endocapillary hypercellularity (p = 0.279),

segmental glomerulosclerosis (p = 0.569), tubular atrophy (p = 0.294), cellular or fibro cellular crescents (p = 0.223) (Table 5).

Table 5: Proteinuria by gender and MEST-C score.

	Proteinuria				
	Non-nephrotic	Nephrotic	None	Total	P value
	No. (%)	No. (%)	No. (%)	No. (%)	
Gender					
Male	85 (75.9)	11 (9.8)	16 (14.3)	112 (100.0)	
Female	43 (78.2)	6 (10.9)	6 (10.9)	55 (100.0)	0.824*
M					
0	91 (76.5)	10 (8.4)	18 (15.1)	119 (100.0)	
1	37 (77.1)	7 (14.6)	4 (8.3)	48 (100.0)	0.289*
E					
0	93 (76.9)	10 (8.3)	18 (14.9)	121 (100.0)	
1	35 (76.1)	7 (15.2)	4 (8.7)	46 (100.0)	0.279*
S					
0	38 (73.1)	5 (9.6)	9 (17.3)	52 (100.0)	
1	90 (78.3)	12 (10.4)	13 (11.3)	115 (100.0)	0.569*
T					
0	75 (78.1)	11 (11.5)	10 (10.4)	96 (100.0)	
1	34 (77.3)	5 (11.4)	5 (11.4)	44 (100.0)	
2	19 (70.4)	1 (3.7)	7 (25.9)	27 (100.0)	0.294**
C					
0	106 (77.9)	15 (11.0)	15 (11.0)	136 (100.0)	
1	22 (71.0)	2 (6.5)	7 (22.6)	31 (100.0)	0.223**
Total	128 (76.6)	17 (10.2)	22 (13.2)	167 (100.0)	

*By Chi square test. **By Fisher's exact test.

It is evident in table 6 that there was no significant association between gender and the prevalence of hypertension ($p = 0.585$). The majority (73.9%) of patients with M0 had hypertension, compared with 54.2% of patients with M1 ($p = 0.013$). No significant association was detected between hypertension with endocapillary hypercellularity

and segmental glomerulosclerosis ($p = 0.602$, and $p = 0.106$ respectively). The table shows that the more advanced the tubular atrophy, the more the rate of hypertension ($p = 0.002$). No significant association was detected between cellular or fibro cellular crescents and hypertension ($p = 0.720$) (Table 6).

Table 6: Hypertension by gender and MEST-C score.

	Hypertension		Total	p
	Yes	No		
	No. (%)	No. (%)	No. (%)	
Gender				
Male	78 (69.6)	34 (30.4)	112 (100.0)	
Female	36 (65.5)	19 (34.5)	55 (100.0)	0.585*
M				
0	88 (73.9)	31 (26.1)	119 (100.0)	
1	26 (54.2)	22 (45.8)	48 (100.0)	0.013*
E				
0	84 (69.4)	37 (30.6)	121 (100.0)	
1	30 (65.2)	16 (34.8)	46 (100.0)	0.602*
S				
0	31 (59.6)	21 (40.4)	52 (100.0)	
1	83 (72.2)	32 (27.8)	115 (100.0)	0.106*
T				
0	55 (57.3)	41 (42.7)	96 (100.0)	
1	36 (81.8)	8 (18.2)	44 (100.0)	
2	23 (85.2)	4 (14.8)	27 (100.0)	0.002*
C				
0	92 (67.6)	44 (32.4)	136 (100.0)	
1	22 (71.0)	9 (29.0)	31 (100.0)	0.720*
Total	114 (68.3)	53 (31.7)	167 (100.0)	

*By Chi square test.

It is evident in Table 7 that there were no significant differences between males and females regarding the distribution (or severity) of the following components of the MEST-C score ($p = 0.944$ for M; $p = 0.246$ for E; $p = 0.756$ for S; and

$p = 0.349$ for C). Regarding tubular atrophy, the majority (70.9%) of the females were of the T0 stage, compared with 50.9% of males. While 19.6 % of males were of T2 stage, compared with 9.1% of females (Table 7).

Table 7: MEST-C score by gender.

	Male		Female		Total		p
	No.	(%)	No.	(%)	No.	(%)	
M							
0	80	(71.4)	39	(70.9)	119	(71.3)	
1	32	(28.6)	16	(29.1)	48	(28.7)	0.944*
E							
0	78	(69.6)	43	(78.2)	121	(72.5)	
1	34	(30.4)	12	(21.8)	46	(27.5)	0.246*
S							
0	34	(30.4)	18	(32.7)	52	(31.1)	
1	78	(69.6)	37	(67.3)	115	(68.9)	0.756*
T							
0	57	(50.9)	39	(70.9)	96	(57.5)	
1	33	(29.5)	11	(20.0)	44	(26.3)	
2	22	(19.6)	5	(9.1)	27	(16.2)	0.041*
C							
0	89	(79.5)	47	(85.5)	136	(81.4)	
1	23	(20.5)	8	(14.5)	31	(18.6)	0.349*
Total	112	(100.0)	55	(100.0)	167	(100.0)	

*By Chi square test.

The means of BMI didn't differ significantly between patients with MO and M1 ($p = 0.055$), E0 and E1 ($p = 0.634$), and S0 and S1 ($p = 0.732$). Regarding tubular atrophy, the more the severity of atrophy, the more the mean BMI, but the difference was not significant between the groups ($p = 0.244$). No significant association was found between BMI and cellular or fibro cellular crescents ($p = 0.657$). The mean BMI of those with hypertension (23.89

Kg/m²) was significantly ($p = 0.019$) higher than the BMI of normotensive patients (22.31kg/m²). The highest mean BMI (25.85 Kg/m²) was among nephrotic patients, which was significantly higher than the means of non-nephrotic patients (23.14 Kg/m²), and mean of patients with no protein-urea (22.9 Kg/m²). No significant association was found between BMI and hematuria ($p = 0.271$) (Table 8).

Table 8: Mean BMI by indicators of severity of IgA nephropathy.

	N	Mean BMI	(SD)	p	Groups	P**
M						
0	119	23.77	(4.34)	0.055†		
1	48	22.43	(3.22)			
E						
0	121	23.48	(4.61)	0.634†		
1	46	23.14	(2.20)			
S						
0	52	23.23	(2.94))	0.732†		
1	115	23.46	(4.52)			
T						
0	96	22.94	(3.07)		0 X 1	0.190
1	44	23.91	(4.07)	0.244*	0 X 2	0.174
2	27	24.15	(6.57)		1 X 2	0.814
C						
0	136	23.32	(3.35)	0.657†		

IGA NEPHROPATHY IN ERBIL

I	31	23.68	(6.45)			
HTN						
Yes	114	23.89	(4.41)	0.019†		
No	53	22.31	(3.06)			
Protein-urea						
A) Non-nephrotic	128	23.14	(4.09)		A X B	0.010
B) Nephrotic	17	25.85	(5.54)	0.030*	A X C	0.792
C) None	22	22.90	(1.40)		B X C	0.024
Hematuria						
A) Micro	64	22.86	(3.40)		A X B	0.719
B) Macro	33	23.17	(3.68)	0.271*	A X C	0.115
C) None	70	23.98	(4.77)		B X C	0.352
Total	167	23.39	(4.09)			

†By unpaired t test. *By ANOVA. **By post-hoc test (LSD).

DISCUSSION:

IgA nephropathy is the most common primary glomerular disease in the world but there is variation in its geographical distribution and its prevalence varies among different geographical regions.⁽¹²⁾ The numbers vary greatly in different regions from as low as 5% in the middle east, to 10-35% in Europe, and up to 50% in Japan and China.⁽⁶⁾ In our study the prevalence of IgA nephropathy among native biopsies throughout the study period was 6.3% approximating its prevalence in other studies^(13,14). There is an uneven gender distribution of IgA nephropathy occurrence in various regions. In Europe and North America, the disease predominantly affects males. and male-to-female in Europeans is as high as 3:1. while this ratio is about 1:1 in East Asia. In our study, IgA nephropathy is more common among males (67.1%) than in females (32.9%) which is similar to the results of previous studies^(15,16,17). IgA nephropathy is seen in all age groups of our study but is most prevalent in the third and fourth decades of life. The mean age was 34.03, per other studies^(14,16,17). Regarding the clinical features of patients at the time of biopsy, in our study, We found that hypertension was present in 68.3% of the patients and it was the most common symptom in our patients this finding is similar to that previous studies 67.9%⁽¹⁶⁾, 65%⁽¹⁸⁾, 84.1%⁽¹⁹⁾. Edema was present in 51.5% of our patients, a similarly high percentage was found in other studies 65.1%⁽¹⁶⁾, and 46.5%⁽¹⁹⁾. Macro hematuria was present in 19.8% of patients, other studies also

showed a low incidence of 11.3%⁽¹⁶⁾, 10%⁽¹⁹⁾, 19%⁽²⁰⁾, 17%⁽²¹⁾, 19%⁽²²⁾, 4%⁽²³⁾, and 17.4%⁽¹³⁾. Microscopic hematuria was found in 38.3% a similar low percent was found in a previous Chinese study 13.7%⁽²⁰⁾ and a study in Hong Kong 25%⁽²²⁾. Whereas other studies showed a much higher percentage of microscopic hematuria was seen in other studies, 48%⁽²³⁾, 82.6%⁽¹³⁾, 95.8%⁽²⁴⁾. Subnephrotic proteinuria was found in 76.6% of other studies and showed a similarly high percentage, 60.4%⁽¹⁶⁾, and 81.25%⁽²⁴⁾. Nephrotic proteinuria was much less common 10.2% among our patients a similar finding was found in other studies 21.7%⁽¹⁶⁾, and 18.75%⁽²⁴⁾. Renal impairment was seen in 49.7% of our patients. Similar findings were seen in other studies 50.7%⁽¹³⁾, and 47.6%⁽²¹⁾. Renal impairment was more common in males than females (p-value < 0.016) this finding was in agreement with previous studies^(25,26). Clinicopathological correlation was done between clinical variables and the degree of pathological changes as MEST-C score, regarding mesangial hypercellularity, renal impairment was significantly associated with M0 (P value < 0.001) No significant association was found between M score and renal function decline in previous studies^(16,27, 28,30,31). Correlating with the degree of sclerosis, there is a statistically significant positive association of renal impairment with S1 (P value < 0.003). a similar finding is seen in other studies⁽¹⁶⁾. Also the significant

association of Renal impairment with the T score (P value <0.001) this finding is in agreement with other previous studies^(18,27,28). Renal impairment was associated with crescent (the severity of C score) but not statistically significant (p-value 0.068) which is in agreement with other studies.⁽²⁷⁾ whereas a significant association was found in a previous study⁽³⁴⁾ Correlating hematuria with gender No significant association was found P value; of 0.214 which is different from other studies like⁽³²⁾. A significant association was found between hematuria and M1 (P= value0.029). A similar finding was observed in the study⁽³³⁾, but different from⁽³⁴⁾. Significant association of hematuria and severity of T score (P value <0.001), which is similar to a previous Indian study⁽³⁴⁾ but differs from a previous Chinese study⁽³³⁾. No significant association between hematuria and E differs from other previous studies^(33,34). No significant association between hematuria and S, a finding similar to previous studies^(33,34). No significant association between hematuria and C differs from previous studies^(33,34). Correlating of proteinuria with gender No significant association was found P value=0.824 which is different from a previous Chinese study⁽³²⁾. No significant association between proteinuria and MEST C score. A previous Indian study⁽³⁴⁾ showed a significant correlation between proteinuria only with T score. Correlating hypertension with gender No significant association was found (P value=0.585) which differs from a previous Chinese study⁽³²⁾. A significant association was found between hypertension and M1 (P value=0.013) and T score (P value=0.004). No significant association between hypertension and elements of MEST C score⁽¹⁶⁾ was found a significant association of E score and S score with hypertension. Regarding the distribution of MESTC score in our patients, M0 in our study comprised 71.3% and M1 28.7% ,E0 was 72.5% ,E1 was 26.9%. S0 was 31.1% and S1 was 68.9%, T0 was 57.5%, T1 was 26.3%, T2 was 14.4%. Similar values were obtained in other studies⁽²⁷⁾. There were no statically significant differences in the frequency of the MEST C score between males and females apart from the T score. Similar findings were observed in other studies⁽³⁵⁾. Another study showed a significant association of the male gender with T and S scores⁽³⁶⁾. Correlating BMI with clinical and histological features of IgA nephropathy. There was a significant association between Higher

BMI and hypertension and proteinuria. Similar results were seen in previous studies^(37,38,39). No significant association between BMI and elements of the MEST C score, similar findings were seen in a previous Chinese study.⁽⁴⁰⁾ Our study has limitations including the fact that it was a retrospective, single-center, hospital-based study, which means that only patients who presented to our hospital were evaluated and biopsied. The retrospective nature and absence of long-term follow-up are other factors.

CONCLUSION:

The prevalence of IgA nephropathy in our study was 6.3%. Hypertension and renal impairment were common presentations in our patients. Renal impairment was significantly associated with tubulointerstitial fibrosis and segmental sclerosis. Male patients had more incidence of renal impairment and more tubulointerstitial fibrosis in the biopsy. Increased BMI was associated with a higher incidence of hypertension and proteinuria. More studies with prospective nature and larger sample size and required to confirm our findings.

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