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IgA Nephropathy in Northern Jordan: Evaluation Using the MEST-C Score of Oxford Classification System

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Abstract

IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide. However, predicting prognosis from the histopathological evaluation of a tissue biopsy has not been well-established until recently. The aim of this research is to evaluate IgAN patients in Northern Jordan by the MEST-C score of Oxford Classification System. Clinical data and histopathology reports of twenty-seven patients diagnosed with IgAN were retrospectively reviewed. These data were retrieved from the electronic health information system of King Abdullah University hospital. The results showed a male predominance (70 %) and a mean age of (24 ± 16) years at diagnosis. MEST-C Oxford classification was as follows: five (18.5 %) patients had mesangial hypercellularity (M1), six (22.2 %) patients had endo-capillary hypercellularity (E1), eight (29.6 %) patients had segmental glomerulosclerosis (S1), four (14.8 %) patients had interstitial fibrosis/tubular atrophy (IFTA) score of (T1) and (0 %) had a score of (T2). As for crescents, three (11.1 %) had (C1) and one (3.7 %) had (C2). A significant negative correlation was found between the final estimated glomerular filtration rate (eGFR) at follow-up and the total MEST-C score (Spearman's Rho = 0.460, $p<0.05$). Histopathological parameters represented by the MEST-C Score of Oxford Classification can predict outcome in the study's cohort, and is similar to previous published studies.

Keywords: IgA Nephropathy, MEST-C score, Oxford classification, Northern Jordan.

1. Introduction

IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide (D'Amico, 1987). Its prevalence is notably high in South East Asia, where IgAN is the diagnosis in 30–50 % of renal biopsies (Schena, 1990). Clinical presentation of IgAN ranges from persistent microscopic hematuria to a rapidly progressive renal failure, but its progression is generally slow with up to a 30 % of the patients progressing to end-stage renal disease (ESRD) within twenty years (D'Amico *et al*., 1987; Moriyama *et al*., 2014).

Nephrologists use clinical information to identify major risk factors for the progression of IgAN to distinguish cases of IgAN that carry a good prognosis from those who exhibit a progressive course and eventually might need renal replacement therapy. These risk factors include age, the extent of proteinuria, low glomerular filtration rate at first presentation, and hypertension (D'Amico, 2004)

On the other hand, predicting prognosis from the histopathological evaluation of a tissue biopsy has not been well-established until recently. Oxford Classification of IgA nephropathy is the most accepted classification and the most utilized one by practicing nephropathologists. This system identifies the following key predictors in the biopsy that can serve as prognostic markers, (MEST-C score): M, mesangial hypercellularity; E, endocapillary proliferation; S, segmental glomerulosclerosis and/or adhesion; T, tubular atrophy and interstitial fibrosis; and C, cellular or fibrocellular crescents. Each of the previous histologic parameters was found to be independently associated with a clinical renal outcome (Cattran *et al*., 2009; Roberts *et al*., 2009; Trimarchi *et al*., 2017).

The aim of this study is to describe the histopathologic features of IgAN patients in Northern Jordan using MEST-C score of Oxford classification system of IgAN, and to report the correlation between the histopathological lesions and clinical presentation at the time of the renal biopsy and on follow-up.

2. Patients and Methods

Twenty-seven kidney biopsies for twenty-seven patients were reviewed. All cases were presented to King Abdullah University Hospital, Irbid, Jordan, and have been diagnosed with primary IgAN in the period between 2004 and 2017. The diagnosis of IgA nephropathy was confirmed by Hematoxylin and eosin stain (H&E) histological examination and by Immunofluorescence studies. Patients with a clinical history of Henoch Schonlein purpura and renal biopsies with fewer than six

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identifiable glomeruli were excluded from the study. All cases were reviewed and scored using the MEST-C score of the Oxford Classification of IgAN (Cattran *et al.*, 2009; Trimarchi *et al.*, 2017). Clinical and laboratory data were retrieved from King Abdullah University hospital medical records. Laboratory tests carried out at time of diagnosis included urine dipstick protein, serum creatinine and eGFR (estimated Glomerular Filtration Rate), calculated by Chronic Kidney Disease Epidemiology equation (CKD-EPI equation) and were recorded. Serum creatinine and eGFR were available for twenty-three patients only and the same tests were repeated on follow-up. Proteinuria was measured using the protein dipstick test and was available for twenty-two patients only at the time of the diagnosis and on follow- up. This study was approved by the Institutional Review Board of Deanship of Research at Jordan University of Science and Technology under research grant number 20180225.

2.1. Statistical Analysis:

The mean values and standard deviations were calculated, and the statistical significance of the differences between groups was calculated using independent t test and Chi-square. The Spearman's co-efficient of correlation was used to check the correlation between the total MEST-C score and the final e-GFR. SPSS IBM 23 was used for statistical analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients' Characteristics

Among the twenty-seven patients, nineteen (70.4 %) were males and eight (29.6 %) were females. The patients' age ranged from one year to sixty-six years with a mean of ± SD of 24.0 ± 16.7 (median = 21). The follow-up period ranged from 1.2 months to 13.3 years. The mean age of females was 22.9 (± 17.9), while the mean age of males was 24.4 (±16.6). Table 1 summarizes the baseline characteristics of the twenty-seven patients.

Table 1. Baseline characteristics of the study cohort of 27 patients with IgA nephropathy**.**

Variable	N (%)
Age, mean ±SD	24.0 ± 16.7
Sex: Male	19 (70.4%)
Female	8 (29.6%)
Follow up,(Years), mean ±SD	3.9 ± 3.7
eGFR ml/min/1.73m^2, mean ±SD	90 ± 47.4

eGFR: estimated glomerular filtration rate

3.2. Clinical Features and Laboratory Results at Presentation and During Follow –up.

In the study's small cohort, the patients' age (P=0.03), not their sex (P=0.62), had an effect on eGFR. The mean serum creatinine level for the twenty-three patients was 107.7µmol/L ± 97.7 with a median of 74 µmol/L. The mean ± S.D serum creatinine for the females was 136.3 µmol/L ± 158 (median 63), while that of males was 95.3 µmol/L ± 58.8 (median=76.5). The eGFR at diagnosis was 90 mL/min ± 47.4 (median=89). Proteinuria detected by dipstick urine analysis showed a significant effect on eGFR (P=0.046); one patient (4.5 %) showed trace, five (22.7 %) had a score of 1+, 3 (13.6 %) a score of 2+ and 8 (36.4 %) a score of 3+, while no protein was found in five patients (22.7 %).

The eGFR at follow-up had a mean value of 91.7 ml/min ± 44.5 (median=98). Serum creatinine at follow-up had a mean value of 132.4 µmol/L ± 163.1 (median=69). As for the twenty-two patients with a record of proteinuria, on follow-up, nine showed no proteinuria (40.9 %), one showed trace (4.5 %), five showed 1+ (22.7 %), six showed 2+ (27.3 %) and one showed 3+ (4.5 %).

Out of the twenty-three patients, five (21.7 %) patients had chronic kidney disease (CKD) stages 3-5 (eGFR<60 mL/min/1.73m^2) at presentation, three (60 %) were males and two were females (40 %). Their mean age was 27±14.2 (median=33).The clinical characteristics and MEST-C score classification for these five patients is summarized in Table 2. During follow-up, two (8.7 %) patients developed CKD (stages 3-5) (eGFR<60 mL/ min/ 1.73m^2) upon a follow-up period of four to five years; their mean age was 43.5±31.8 and both were males. Their mean serum creatinine at diagnosis was 115.5 µmol/L ±26.2, and the serum creatinine on follow-up had a mean of 322.5 µmol/L ± 238.3. Their MEST-C scores were (M0, E0, S1, T1, C0) and (M0, E1, S1, T0, C1), respectively.

Although the mean age of patients with C0 score was lower than the mean age of those with a C1 score (21 years for C0 VS 41 years for C1), the difference was not statistically significant (P=0.056). In an attempt to correlate the total MEST-C score to laboratory parameters, the score variables were added together, producing a total score for each patient, and this value was correlated with the laboratory findings. A significant negative correlation was found between the final eGFR at follow-up, and the total MEST-C score (Spearman's Rho =0.460, P<0.05). It seems that those who initially had extensive involvement of glomeruli on initial biopsy end up with a worse prognosis as reflected by their low eGFR at follow-up. Older patients were found to have lower eGFR (Spearman Rho=-0.475, P<0.05) and higher creatinine (Spearman Rho=0.576, P<0.05) levels at follow-up. The Chi Square test yielded a significant association between the degree of interstitial fibrosis and tubular atrophy (IFTA) and segmental glomerulosclerosis (P<0.05).

3.3. MEST-C Score

MEST-C Scoring System was performed on all the twenty-seven renal biopsies; the number of glomeruli ranged between six and fifty-five with a median of fourteen glomeruli per biopsy. Mesangial hypercellularity was found in all biopsies, twenty-two (81.5 %) in 50 % of glomeruli or less (M0) and five (18.5 %) patients had mesangial hypercellularity in greater than 50 % of the glomeruli (M1). Twenty-one (77.8 %) had E0 and six (22.2%) patients had endocapillary hypercellularity (E1). Nineteen (70.4 %) had a score of S0, while eight (29.6 %) had a score of S1. twenty-three (85.2 %) had a score of T0, four had T1 (14.8 %) and no cases had T2 (0 %). As for crescents, twenty-three (85.2 %) had a score of C0, three (11.1 %) had C1 and one had C2 (3.7 %). Table 3 summarizes the clinical and histological variables in the renal biopsies of the twenty-seven patients with comparison with other studies.

Table 2. Clinicopathologic characteristics of the 5 patients with CKD stage (3-5) at presentation.

Clinicopathologic variable	Value
Age at presentation mean ±SD	27±14.2
Male : Female	3:2
Mean serum creatinine at diagnosis	115.5 μmol/L±26.2
Mean serum creatinine at follow up	322.5 μmol/L±238.3
Mesangial hypercellularity score	
≤0.5 (M0)	4(80%)
>0.5 (M1)	1(20%)
Endocapillary hyercellularity score	
Absent (E0)	4(80%)
Present (E1)	1(20%)
Segmental glomerulosclerosis	
Absent (S0)	2(40%)
Present (S1)	3(60%)
Tubularatrophy/interstitial score	
≤25% (T0)	2(40%)
26-50% (T1)	3 (60%)
>50% (T2)	0(0%)
Crescents	
Absent (C0)	4(80%)
≤25% (C1)	1(20%)
>25% (C2)	0(0%)

CKD, chronic kidney disease

Table 3. A comparison of both the clinical and histopathological parameters in the current study and the largest cohorts for patients with IgA nephropathy.

Variables	Our study	Oxford cohort* (2009)	Zeng *et al** (2012)	Moriyama *et al* (2014)	VALIGA cohort (2014)
Age (mean ±SD, years)	24±16	30 (4–73)†	34 (18-73)†	33±12	36±16
Sex M:F	60:40	72:28	50:50	40:60	73:27
Follow-up (mean, years)	3.83±3.7	5 (1–22)†	4.4(0.6-14)†	7.9±7.1	4.7(2.4-7.9)†
eGFR initially (mL/min/1.73m2)	90±47	83±36	85 ±32	78.5±26	73±30
CKD (stage 3-5) at presentation	21.7 %	*	*	24%	37%
Progression to CKD or ESRD	8.7%	22%, 13%¥	15%, 8.8%¥	-	14%, 12%¥
MEST-C Score at diagnosis					
M1	18.5%	81%	43%	47.6%	28%
E1	22.2%	42%	11%	44.3%	11%
S1	29.6%	76%	83%	74.6%	70%
T1	14.8%	30%	24%	23.0%	17.4%
T2	0%	5%	3.3%	5.8%	3.6%
C1	11.1%	-	48%‡	6.7%‡	11%‡
C2	3.7%	-	2.4%	-	-
Total number of patients	27	256	1026	1012	1147

eGFR, estimated glomerular filtration date; CKD, chronic kidney disease; ESRD, end-stage renal disease, M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy and interstitial fibrosis; C, crescents

** Inclusion criteria were an initial (eGFR) >30 mL/min/1.73 m2 and an initial proteinuria with protein excretion >0.5 g/24 h.*

† Median.

¥ The two numbers represent 50% decrease in eGFR (%) and ESRD (<15ml/min per 1.73m2) (%) respectively;

‡ C1 or C2.

4. Discussion

IgAN is the most common type of glomerulonephritis worldwide (D'Amico, 1987). Although IgAN is slowly progressive, it is not a benign disease. There have been several classification systems suggested in the past in an attempt to improve the capability to predict the outcome of the patients and guide their therapy (Alamartine *et al*., 1990; Haas, 1997; Katafuchi *et al.*, 1998; H. Lee *et al*., 2012; Radford *et al.*, 1997; Wakai *et al*., 2006).

Since 2009, the Oxford classification of IgAN has been widely used and accepted by both pathologists and nephrologists. It has been proven in many studies that the pathological features: mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulus-clerosis and the extent of tubular atrophy/interstitial fibrosis are independently predictive of the clinical outcome (Cattran *et al.*, 2009; Coppo *et al*., 2014; Roberts *et al.*, 2009).

Furthermore, Barbour *et al* (Barbour *et al*., 2016), using a large international cohort, examined whether combining the MEST score with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than the current best methods that use two years of follow-up data. Their work showed that the combination of MEST score with readily available blood pressure, proteinuria, and eGFR at the time of biopsy predicted the composite renal outcome similar to using clinical data over two years of follow-up.

The patients' age in the present study had a mean of twenty-four years old at presentation with nearly 30 % of them being ten years of age or younger. Similar results have been shown by D'Amico *et al* (2004) who reviewed the largest IgAN studies in the literature; six of them from Europe, Asia and North America. The mean age in their study ranged between twenty-two and twenty-seven years old. On the other hand, in the present study, the mean age at presentation is slightly lower than that of the largest three cohorts of IgAN in the literature (Coppo *et al*., 2014; Moriyama *et al*., 2014; Zeng *et al.*, 2012) with the mean age ranging between thirty-three and thirty-six years.

In North American studies of IgAN, the male to female ratio was about 2:1 for children and adults (Wyatt *et al*., 1998). In addition, most studies on Caucasian population showed male predominance (Coppo *et al.*, 2014; Galla, 1995; Schena, 1990), whereas the ratio is nearly 1:1 in Asia (Le *et al.*, 2012; Lee *et al*., 2012; Moriyama *et al*., 2014; Zeng *et al*., 2012). The current study also found also male predominance as shown by North American and Caucasian series.

This study found that about 30 % of the patients with CKD of the stages three to five (eGFR<60 mL/min/1.73m^2) at the time of diagnosis were above thirty years old. But, if all age groups included; this percentage will go down to 21.7 %, with a male predominance and a mean age of twenty-seven years at the presentation. This percentage is lower than that of the large VALIGA cohort (n = 1147), including mostly Italian patients, where they found that 37 % of their patients presented with CKD at the stage three to five (Coppo *et al.*, 2014).

Older patients were found to have lower eGFR and higher serum creatinine levels at follow-up in this study. Having said that, it is known that a slight increase in the eGFR is expected at an advanced age due to anatomical,

functional and physiological changes in the aging kidneys (Douville *et al.*, 2009; Glassock and Rule, 2012). Moriyama *et al* (Moriyama *et al*., 2014) showed that old age at presentation using univariate analysis is associated with the risk of progression to an end-stage renal disease. But the multivariate Cox regression analysis showed that it was insignificant, and so was the factor of being male (Moriyama *et al.*, 2014). Moreover, it was shown that both the older age at presentation and being a male are weak predictors as clinical prognostic factors according to the most accurate studies in the literature analyzed by D'Amico (D'Amico, 2004).

During initial follow-up, clinical indicators as urine dipstick protein levels showed improvement with various treatments, where (36.4 %) of the patients had a score of 3+, and only (22.7 %) had no protein in their urine at presentation. During further follow-up only (4.5 %) showed 3+ urine protein level and about (41 %) showed no proteinuria. Cattran *et al* and the Oxford Group had an improvement in proteinuria on follow-up, with proteinuria of 1.7 (0.5–18.5) g/day at the time of biopsy and 1.1 (0.1–9.3) g/day levels on follow-up (Cattran *et al.,* 2009). So did the VALIGA cohort, with proteinuria of 1.3 (0.6–2.6) g/day at the time of biopsy and 0.8 (0.4–1.6) g/day levels on follow-up (Coppo *et al.,* 2014). Zeng *et al.,* (2012) found also similar values.

In any kind of injury (including immune-complexes as in IgA Nephropathy), an inflammatory response is initiated (as hypercellularity or crescent formation) as a healing process that may lead to renal recovery without significant damage, or to glomerular scars and / or interstitial fibrosis with clinical manifestation of worsening renal function(Lee and Kalluri, 2010)

Regarding the Oxford MEST-C classification, our renal biopsies showed the following percentages: five (18.5 %) patients had mesangial hypercellularity in greater than 50 % of the glomeruli (M1), six (22.2 %) patients had endocapillary hypercellularity (E1), eight (29.6 %) patients had segmental glomerulosclerosis (S1), four (14.8 %) patients had interstitial fibrosis/tubular atrophy score of (T1) and (0 %) had a score of (T2). As for crescents, three (11.1 %) had (C1) and one (3.7 %) had (C2). A comparison of the current results with the Oxford cohort (Cattran *et al.*, 2009; Roberts *et al.*, 2009) and the largest three cohorts reported in the literature for patients with IgAN(Coppo *et al*., 2014; Moriyama *et al.*, 2014; Zeng *et al*., 2012) is shown in Table 3, with both clinical and histopathological data included.

Although clinical data in this study, including initial eGFR, initial CKD (stages 3-5) patients and progression to CKD or ESRD upon follow-up showed lower percentages than those provided by the aforementioned cohorts, these relatively milder clinical presentations are consistent with a milder MEST-C Oxford classification scores than most of the scores provided by the same cohorts.

The present study showed that those who initially had extensive involvement of glomeruli on initial biopsy end up with worse prognosis as reflected by their low eGFR at follow-up. In fact, this is consistent with the Oxford group results (Cattran *et al*., 2009; Roberts *et al.*, 2009) that were validated in the much larger VALIGA cohort - that also came with less restricted inclusion criteria – where they showed that histological signs of chronic and irreversible damage had the strongest association with an unfavorable outcome (Coppo *et al.*, 2014).

The present study had the following limitations; first, it is a retrospective observational review. Second, though the selected center is a tertiary referral teaching hospital, the number of patients included is relatively small (only 27 patients) and larger numbers should be included in future studies.

5. Conclusion

This is the first–ever study of IgA nephropathy profile in a single tertiary referral teaching hospital in Northern Jordan. It showed that histopathological damage of the glomeruli using the MEST-C Score of Oxford Classification, age of the patients, and proteinuria are associated with a worse outcome. The selected patients showed milder MEST-C scores than most of the scores provided by the large cohorts.

Future studies with a larger number of patients and including different geographic areas in Jordan are recommended. These studies might highlight the possibility of familial clustering and geographic variations which can be further compared with profiles from the Levant region.

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References

Alamartine E, Sabatier J Cand Berthoux F C. 1990. Comparison of pathological lesions on repeated renal biopsies in 73 patients with primary IgA glomerulonephritis: value of quantitative scoring and approach to final prognosis. *Clin Nephrol.*, **34(2)**: 45-51.

Barbour S J, Espino-Hernandez G, Reich H N, Coppo R. Roberts I S, Feehally J, Herzenberg A M and Cattran D C. 2016. The MEST score provides earlier risk prediction in lgA nephropathy. *Kidney Int.*, **89(1)**: 167-175.

Cattran D C, Coppo R, Cook H T, Feehally J, Roberts I S, Troyanov S, Alpers C E, Amore A, Barratt J, Berthoux F, Bonsib S, Bruijn J A, D'Agati V, D'Amico G, Emancipator S, Emma F, Ferrario F, Fervenza F C, Florquin S, Fogo A, Geddes C C, Groene H J, Haas M, Herzenberg A M, Hill P A, Hogg R J, Hsu S I, Jennette J C, Joh K, Julian B A, Kawamura T, Lai F M, Leung C B, Li L S, Li P K, Liu Z H, Mackinnon B, Mezzano S, Schena F P, Tomino Y, Walker P D, Wang H, Weening J J, Yoshikawa N and Zhang H. 2009. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int.*, **76(5)**: 534-545.

Coppo R, Troyanov S, Bellur S, Cattran D, Cook H T, Feehally J, Roberts I S, Morando L, Camilla R, Tesar V, Lunberg S, Gesualdo L, Emma F, Rollino C, Amore A, Praga M, Feriozzi S, Segoloni G, Pani A, Cancarini G, Durlik M, Moggia E, Mazzucco G, Giannakakis C, Honsova E, Sundelin B B, Di Palma A M, Ferrario F, Gutierrez E, Asunis A M, Barratt J, Tardanico Rand Perkowska-Ptasinska A. 2014. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int.*, ***86*(4)**: 828-836.

D'Amico G. 1987. The commonest glomerulonephritis in the world: IgA nephropathy. *Q J Med.*, **64(245)**: 709-727.

D'Amico G. 2004. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. *Semin Nephrol.*, **24(3)**: 179-196.

D'Amico G, Colasanti G, Barbiano di Belgioioso G, Fellin G, Ragni A, Egidi F, Radaelli L, Fogazzi G, Ponticelli CandMinetti L. 1987. Long-term follow-up of IgA mesangial nephropathy: clinico-histological study in 374 patients. *Semin Nephrol.,* **7(4):** 355-358.

Douville P, Martel A R, Talbot J, Desmeules S, Langlois Sand Agharazii M. 2009. Impact of age on glomerular filtration estimates. *Nephrol Dial Trans.*, **24(1)**: 97-103.

Galla J H. 1995. IgA nephropathy. *Kidney Int.*, **47(2)**: 377-387.

[Glassock R Jand Rule A D. 2012. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney Int.,* **82(3)**: 270-277.

Haas M. 1997. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. *Am J Kidney Dis,* **29(6)**: 829-842.

Katafuchi R, Kiyoshi Y, Oh Y, Uesugi N, Ikeda K, Yanase Tand Fujimi S. 1998. Glomerular score as a prognosticator in IgA nephropathy: its usefulness and limitation. *Clin Nephrol.,* **49(1)**: 1-8.

Le W, Liang S, Hu Y, Deng K, Bao H, Zeng Cand Liu Z. 2012. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Trans.*, **27(4)**: 1479-1485.

Lee H, Kim D K, Oh K H, Joo K W, Kim Y S, Chae D W, Kim Sand Chin H J. 2012. Mortality of IgA nephropathy patients: a single center experience over 30 years. *PLoS One,* **7(12)**: e51225.

Lee S Band Kalluri R. 2010. Mechanistic connection between inflammation and fibrosis. *Kidney Int Suppl.*,**(119)**, S22-26.

Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, Itabashi M, Takei T, Uchida Kand Nitta K. 2014. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. *PLoS One,* **9(3):** e91756.

[Radford M G, Jr, Donadio J V, Jr, Bergstralh E Jand Grande J P. 1997. Predicting renal outcome in IgA nephropathy. *J Am Soc Nephrol.*, **8(2)**: 199-207.

Roberts I S, Cook H T, Troyanov S, Alpers C E, Amore A, Barratt J, Berthoux F, Bonsib S, Bruijn J A, Cattran D C, Coppo R, D'Agati V, D'Amico G, Emancipator S, Emma F, Feehally J, Ferrario F, Fervenza F C, Florquin S, Fogo A, Geddes C C, Groene H J, Haas M, Herzenberg A M, Hill P A, Hogg R J, Hsu S I, Jennette J C, Joh K, Julian B A, Kawamura T, Lai F M, Li L S, Li P K, Liu Z H, Mackinnon B, Mezzano S, Schena F P, Tomino Y, Walker P D, Wang H, Weening J J, Yoshikawa Nand Zhang H. 2009. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int.,* **76(5):** 546-556.

Schena F P. 1990. A retrospective analysis of the natural history of primary IgA nephropathy worldwide. *Am J Med.,* **89(2)**: 209-215.

Trimarchi H, Barratt J, Cattran D C, Cook H T, Coppo R, Haas M, Liu Z H, Roberts I S, Yuzawa Y, Zhang Hand Feehally J. 2017. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int.,* **91(5)**: 1014-1021.

Wakai K, Kawamura T, Endoh M, Kojima M, Tomino Y, Tamakoshi A, Ohno Y, Inaba Yand Sakai H. 2006. A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. *Nephrol Dial Trans.,* **21(10):** 2800-2808**.**

Wyatt R J, Julian B A, Baehler R W, Stafford C C, McMorrow R G, Ferguson T, Jackson E, Woodford S Y, Miller P Mand Kritchevsky S. 1998. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. Central Kentucky Region of the Southeastern United States IgA Nephropathy DATABANK Project. *J Am Soc Nephrol.,* **9(5)**: 853-858.

Zeng C H, Le W, Ni Z, Zhang M, Miao L, Luo P, Wang R, Lv Z, Chen J, Tian J, Chen N, Pan X, Fu P, Hu Z, Wang L, Fan Q, Zheng H, Zhang D, Wang Y, Huo Y, Lin H, Chen S, Sun S, Wang Y, Liu Z, Liu D, Ma L, Pan T, Zhang A, Jiang X, Xing C, Sun B, Zhou Q, Tang W, Liu F, Liu Y, Liang S, Xu F, Huang Q, Shen H, Wang J, Shyr Y, Phillips S, Troyanov S, Fogo Aand Liu Z H. 2012. A multicenter application and evaluation of the oxford classification of IgA nephropathy in adult chinese patients. *Am J Kidney Dis.,* **60(5)**: 812-820.