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## Risk stratification and long-term kidney survival in IgA nephropathy with particular emphasis on Oxford classification; A narrative review

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### ABSTRACT

**Introduction:** IgA nephropathy (IgAN) is one of the most common forms of glomerulonephritis worldwide. It leads to end-stage renal disease (ESRD) in many patients. At the time of diagnosis, risk stratification is of paramount importance in planning proper management in individual cases. Several studies have been conducted to determine the utility of various demographic, clinical, laboratory, and pathological features on renal biopsy to stratify the risk of disease progression and predict the likely outcome. This review summarizes the emerging data on demographic, clinical, laboratory, and histological prognosis along with risk factors associated with renal outcomes in patients with IgAN.

**Methods:** For this review, we searched DOAJ (Directory of Open Access Journals), PubMed/Medline, Web of Science, Scopus, Embase, and Google Scholar, using keywords including: "IgA nephropathy," "IgA nephritis," "IgAN," "Berger's disease," "Berger's syndrome," "chronic glomerulonephritis," "prognostic factors," "risk factors," "risk stratification," "renal survival," "ESRD," "MEST classification," "MEST-C classification" and "Oxford Classification." To identify other relevant studies, we manually scanned the bibliographic lists of the identified studies and reviewed articles from January 2009 through December 2020. All relevant articles were carefully reviewed, and relevant information was extracted for this narrative review.

**Results:** A total of 152 articles were retrieved from the above literature database searches. The abstracts were carefully reviewed to identify 35 articles containing information on prognostic factors and long-term renal survival in IgAN patients. Relevant information was collected and summarized for this review. The main focus was on using demographic, clinical, and laboratory features, especially serial changes in these parameters during follow-up, for this purpose. Recently a standardized, evidence-based formulation has been devised to evaluate and categorize pathological features on renal biopsy to augment and refine the risk stratification and prognostic value of traditional risk factors; it is popularly known as the Oxford classification of IgAN. There have been numerous validation studies in various ethnic groups that have proven its clinical utility.

**Conclusion:** In conclusion, the clinicians should also take into account the pathologic variables according to the revised Oxford classification in addition to demographic, clinical, and laboratory parameters for early and reliable risk stratification and prognostication in individual patients at the time of diagnosis in IgAN for optimal management and ultimate improvement in long-term outcomes.

#### *Implication for health policy/practice/research/medical education:*

Clinicians should take into account the pathologic variables according to the revised Oxford classification for early, accurate and reliable prognostication in individual patients at the time of diagnosis of IgA nephropathy.

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## Introduction

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, leading to chronic kidney insufficiency in a significant number of cases (1). The disease is ubiquitous; however, it is reported to be more common in people of Asian origin (2). The disease affects individuals of any age; however, it is less frequent in children under five years. The peak incidence of the disease is in the second and third decades of life (3). Macroscopic or microscopic hematuria with or without subnephrotic proteinuria, often associated with the upper respiratory tract infection, is the most common presentation (4). Initially, IgAN was considered a benign disease; however, subsequent studies showed a poor long-term prognosis. The disease is reported to be more aggressive in the Asian population. All of the risk factors for progression of the disease have not been fully elucidated. Some parameters like male gender, high blood pressure, renal failure at presentation, and degree of proteinuria are well-known poor prognostic risk factors. Furthermore, morphologic features on biopsy also have prognostic implications, though these variables have not yet achieved global recognition and application (5).

This glomerulopathy has a broad range of clinical and morphological presentations, leading to difficulties in properly managing the disease (6). The prognosis of this disease is also very heterogeneous. During the past two decades, several studies have been conducted on assessing prognostic factors for disease progression and therapy (7). An accurate prediction of the rate of disease progression is critical for planning optimal management (8).

The clinical course and outcome also vary widely, with nearly one-third of individuals developing the end-stage renal disease (ESRD) 20 years after diagnosis (9). This heterogeneity poses significant challenges in the optimal management, risk stratification, and prognostication of individual patients. It is imperative to identify the potential predictive or prognostic factors for optimal management of the disease to improve long-term renal outcomes.

In this review, we aim to critically analyze and summarize recently published data on demographic, clinical, biochemical, and morphological variables with prognostic implications in patients with IgAN with the main focus on the prognostic relevance of morphological features recommended by the Oxford classification of IgAN following its promulgation in 2009 and revision in 2017.

## Methods (Search strategy)

For this review, we searched DOAJ (Directory of Open Access Journals), PubMed/Medline, Web of Science, Scopus, Embase, and Google Scholar, using keywords including; “IgA nephropathy,” “IgA nephritis,” “IgAN,”

“Berger’s disease,” “Berger’s syndrome,” “chronic glomerulonephritis,” “prognostic factors,” “risk factors,” “risk stratification,” “renal survival,” “ESRD,” “MEST classification,” “MEST-C classification,” and “Oxford Classification.” To identify other relevant studies, we manually scanned the reference lists of the identified studies and reviewed articles from 2009 through 2020. The starting year of 2009 was chosen as this was the year when the original Oxford classification was first published. All relevant articles were carefully reviewed to extract the relevant information for this narrative review.

## Results

A total of 152 articles were retrieved. The abstracts of these articles were carefully reviewed, and 35 relevant articles containing information on prognostic factors and long-term renal survival in IgAN were identified. These articles were studied carefully, and relevant information was collected for this review. The main focus was on using demographic, clinical, and laboratory features (especially their serial measurements during follow-up) for this purpose. In recent years, pathological features on renal biopsy have also been useful in prognostication and risk stratification of individual patients as envisaged in the Oxford classification of IgAN.

## Discussion

IgA nephropathy is a highly heterogeneous disease regarding the renal outcome. About one-third of patients develop a progressive form of the disease, which culminates in ESRD over 20-30 years (10). Therefore, it is essential to identify patients at risk of disease progression earlier in the course of the disease. The demographic, clinical, and laboratory risk factors will be discussed in the first part of this review. This will be followed by a discussion of the pathological features of renal biopsy, which are equally important in predicting the prognosis.

### Demographic, clinical and laboratory risk factors

Numerous studies have been conducted to determine the risk factors for the progression of IgAN to ESRD. Most of those studies have been retrospective and found several demographic, clinical, and laboratory features at the time of biopsy and during follow-up to predict the long-term outcome. Box 1 lists some of the traditional and well-studied prognostic factors in IgAN.

To evaluate the epidemiology and risk factors for the progression of IgAN in a group of Chinese patients, Liu et al, studied 246 biopsy-proven cases of IgAN. They found that male gender, mean arterial blood pressure, hematuria, plasma creatinine, cholesterol, hemoglobin level, Lee classification more than 3, and MEST-C  $\geq 3$  were independent risk factors for low-glomerular

**Box 1.** Some of the traditional demographic, clinical, and laboratory features at presentation and during follow-up are of prognostic value in IgA nephropathy

**Clinical and laboratory features at the time of presentation (cross-sectional data).**

- Male gender
- Proteinuria >1 g/d
- Decreased GFR
- Hypertension

**Clinical and laboratory features during follow-up**

- Persistent proteinuria >1 g/d
- Declining GFR
- Persistent hypertension

filtration rate (low-GFR) in IgAN in China (1). To determine the prognostic value of the Oxford classification morphological data and evaluate the clinicopathologic parameters associated with kidney survival, Jebali et al studied 50 adult patients with IgAN over 10 years. Their mean age was  $35.6 \pm 10.6$  years. In this study, 50% of the participants had high blood pressure, and the median value of proteinuria was 1.9 g/24 h. In addition, the median GFR was 47.6 mL/min/1.73 m<sup>2</sup>. During the median follow-up period of 30 months, 10 (20%) of the participants developed ESRD. This study also showed that high blood pressure, proteinuria, tubular dysfunction, GFR, and Oxford score >3 were linked to progression to ESRD (7). Another retrospective investigation by Yeter et al, on 97 biopsy-proven IgAN patients showed that 13% of participants developed ESRD in 37 months of follow-up. They also concluded that the requirement for renal replacement therapy (RRT), serum creatinine concentration of >1.97 mg/dL, plasma albumin value less than 3.5 g/dL, and proteinuria more than 3.5 g/d, were found to be prognostic indicators of ESRD progression (11). Recently, Jha et al, investigated various demographic and clinical data such as age, gender, presence of hypertension, edema, and hematuria in 48 adult patients with biopsy-proven IgAN at a single tertiary care hospital in India. They showed that 37 (77.08%) of patients with IgAN had kidney failure on presentation. Among all, 39 (81.25%) participants had sub-nephrotic proteinuria, and 9 (18.75%) had nephrotic-range proteinuria. Two (28.57%) participants with nephrotic-range proteinuria and 12 (41.66%) patients with sub-nephrotic proteinuria progressed to ESRD during the follow-up period. However, their follow-up duration was short. They concluded that their cohort of IgAN patients was unique in presentation and showed an aggressive course even on short-term follow-up. Previously, Bagchi et al aimed to investigate the clinical and morphological profile of their 103 IgAN patients. In their patients, the most

common presentation was nephrotic-range proteinuria in 65 (63.1%) patients. There were also 69 (67.0%) cases that had a GFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> (12). Accordingly, ESRD developed in 7 (11.3%) of the patients. However, their follow-up duration was also brief, with a median follow-up of 17.7 months.

To determine the long-term outcome of a large group of pediatric patients with IgAN from China, Wu et al, studied 1243 children with a follow-up period of more than seven years. They found that low initial GFR, degree of proteinuria, hyperuricemia, and hypertension were associated with poor long-term renal outcomes. They concluded that the 15-year kidney survival rate of their pediatric IgAN patients was 84% (13). Another case-control study by Shu et al with 50 ESRD patients who had underlying IgAN as the etiology of their renal failure found that low-baseline eGFR, time-average hemoglobin, and high time-average uric acid were accelerating factors more likely to predispose to the development of ESRD. The study was conducted to find the risk factors of rapidly progressive IgAN, which evolved to ESRD within ten years (14). Other recent studies also confirm that the possibility of development of ESRD in individuals with IgAN is defined by the degree of proteinuria, value of GFR, and the presence of hypertension. A previous study also showed a mean proteinuria of more than 0.5–1 g/d accompanied a poor kidney outcome (15). Sevillano et al followed a cohort of 112 IgAN patients for an interval of  $14 \pm 10.2$  years. This study showed that the proportion of individuals progressing to ESRD or a 50% decrease in kidney function was considerably higher in cases with hematuria than in individuals who had no or minimal hematuria. They also demonstrated that renal function at baseline, time-averaged proteinuria, and time-averaged hematuria were independent risk factors for ESRD development (16). Using a random forest model to predict ESRD in 262 renal biopsy-proven IgAN cases in an Asian cohort (median follow-up time; 4.66 years), Liu et al found that eGFR carried additional value for ESRD prediction in Chinese IgAN patients (17). In a previous study, Zhang et al investigated the distinctive features of acute kidney injury (AKI) in IgAN cases in the Chinese population. They conducted a retrospective analysis of 1512 biopsy-proven primary IgAN patients. Their study showed that the prevalence of AKI in IgAN cases was 9.59%. They interestingly found that most acute renal failure cases were male, elderly, with hyperlipidemia, tobacco use, and hypertension. Other risk factors included preexisting renal failure, higher serum creatinine at presentation in association with higher uric acid levels, and the degree of proteinuria present. In addition, they found that lower serum albumin, lower hemoglobin levels, and late-onset of macroscopic hematuria were also predisposing factors

(18). Several studies suggested a relationship between hematuria with acute renal impairment since in around 25% of cases, renal function did not return to baseline (19). Recently, Imai et al studied 310 individuals with primary IgAN. They found 10- and 20-year kidney survival rates to be 83.6% and 72.5%, respectively. They concluded that hypertension, smoking, and low GFR are independent risk factors for kidney-related death (20). Lee et al, several years ago, also investigated the causes of death of IgAN patients through a single-center study over 30 years. The outcomes of their study were mortality rate and ESRD progression. They demonstrated a mortality rate of 5.3% and progression to an ESRD rate of 20.6% in total. Accordingly, 10-, 20- and 30-year survival rates were 96.3%, 91.8%, and 82.7%, respectively. Interestingly, over 50% of patients' mortality occurred regardless of ESRD development. The overall mortality in IgAN patients was higher than that of the general population. Women and patients with renal risk factors had higher mortality compared to the general population. Importantly, they detected those men had comparable mortality to the general population; however, the death rate was double in women. Lee et al, also found that the presence of renal risk factors such as preexisting kidney failure with GFR <60 mL/min/1.73 m<sup>2</sup> was a risk factor for death. In addition, systolic hypertension and proteinuria >1 g/24 h had raised mortality. They also found that the overall mortality was elevated to 43% as compared to the age/sex-matched general population (21).

In summary, the majority of the above-mentioned studies confirmed the prognostic and predictive value of the standard and well-known demographic, clinical, and laboratory features at presentation or during follow-up and identified some novel parameters that can refine the prognosis in patients with IgAN. Box 2 depicts some of these new parameters. There is a need to further investigate the prognostic and predictive value of these additional risk factors in large multicenter cohorts of patients over prolonged follow-up periods to come up with definitive conclusions.

### Morphological risk factors (MEST scores)

As is well known, kidney biopsy is currently regarded as the gold standard for diagnosis, management, and prognosis of IgAN (22).

Pathologically, IgAN is also heterogeneous and is characterized by significant mesangial IgA deposits in association with proliferation of mesangial cells on light microscopy, accompanied in some cases by endocapillary hypercellularity and/or extracapillary hypercellularity (22). Many studies conducted in the past reported that morphological lesions in IgAN are also the risk factors for progression of this disease. There was, however,

**Box 2.** Some new demographic, clinical, and laboratory features at presentation and during follow-up which are of prognostic value in IgA nephropathy

#### Demographic, clinical and laboratory features at presentation (cross-sectional data).

- Elderly patients
- Smoking
- Pre-existing renal failure
- Late onset of macroscopic hematuria
- Elevated serum creatinine
- Elevated serum lipids
- Elevated serum cholesterol
- Decreased serum albumin
- Elevated serum uric acid
- Blood hemoglobin level
- Hematuria

#### Time-averaged features on follow-up

- Time-averaged hemoglobin level
- Time-averaged proteinuria
- Time-averaged uric acid

little consensus on reporting and categorizing of these features. The Oxford classification was formulated to fill this unmet need of identifying and categorizing morphological lesions with prognostic value on renal biopsy. The initial classification scheme identified four morphologic variables to be of independent prognostic value (23). These include mesangial proliferation (M), endocapillary hypercellularity (E), segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T). In a subsequent revision of the classification, crescents (C) were also included as shown in Table 1 and illustrated in Figures 1-5 (24,25). The Oxford classification of IgAN was primarily formulated with the purpose of identifying the pathologic parameters which are highly reproducible and have independent predictive value for kidney outcomes. This classification of IgAN can evaluate each MEST-C variable separately or a total MEST-C score may be utilized (26). In a recent study by Miyabe et al, employing the total score of Oxford classification (total MEST-C score) named as O-grade for predicting kidney outcome in IgAN, studied 871 IgAN cases. The clinical findings became considerably more severe with increasing O-grades. The study also showed that the mean arterial pressure (MAP), proteinuria at the time of biopsy, GFR, and O-grade were independent parameters predicting kidney outcome. They concluded that the total score of the Oxford classification named as O-grade was associated with kidney prognosis (26).

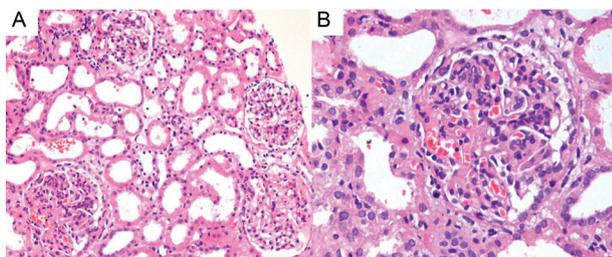
In a study evaluating the morphologic variables in IgAN by Yeter et al, it was shown that glomerulosclerosis involving more than 53% of glomeruli, T2 score and total Oxford-MEST-C score of more than 2 were found to have

**Table 1.** The main pathological parameters that should be reported in pathology reports for patients with IgA nephropathy according to revised Oxford MEST-C classification

Pathological parameters	Scores
<b>Mesangial hypercellularity (M)</b>	
Present in $\leq 50\%$ of the glomeruli	M0
Present in $> 50\%$ of the glomeruli	M1
<b>Endocapillary hypercellularity (E)</b>	
Absent	E0
Present	E1
<b>Segmental glomerulosclerosis (S)</b>	
Absent	S0
Present	S1
<b>Tubular atrophy/interstitial fibrosis (T)</b>	
0–25% of cortical area	T0
26–50% of cortical area	T1
$> 50\%$ of cortical area	T2
<b>Cellular/fibrocellular crescents (C)</b>	
No crescents	C0
Crescents in $< 25\%$ of the glomeruli	C1
Crescents in $\geq 25\%$ of the glomeruli	C2

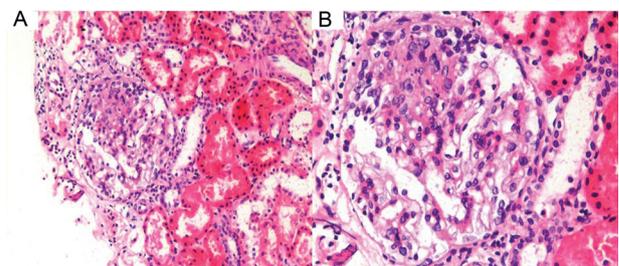
prognostic implications for reaching ESRD (11).

Furthermore, Liu et al showed that a MEST-C score more than 3 was significantly greater in the low-eGFR group (1). Rui et al, recently studied 101 IgAN individuals in a retrospective study. This study showed that M1 and S1 were the risk factors for the effect of immunosuppressive therapy in IgAN patients. They also found that M1 and T2 were independent predictive parameters for poor kidney outcomes. The results from this study imply that M and S scores are independent predictors for outcomes of immunosuppressive treatment, since T and M scores can efficiently predict poor kidney outcomes after immunosuppressive treatment (27). To validate a risk estimation model in Korean IgAN patients, Hwang et al, retrospectively studied 545 biopsy-proven IgAN cases.

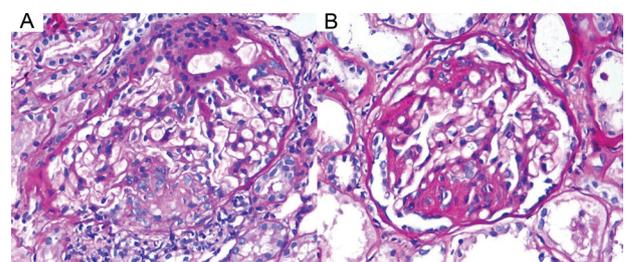


**Figure 1.** (A) A representative biopsy of a patient with IgA nephropathy. Three of the four glomeruli shown in this field show segmental to global mesangial hypercellularity, qualifying this biopsy as M1 according to Oxford classification. Some tubules contain red blood cells signifying hematuria (H&E,  $\times 200$ ). (B) One of the glomeruli shown in A is seen at high magnification with global mesangial hypercellularity (H&E,  $\times 400$ ).

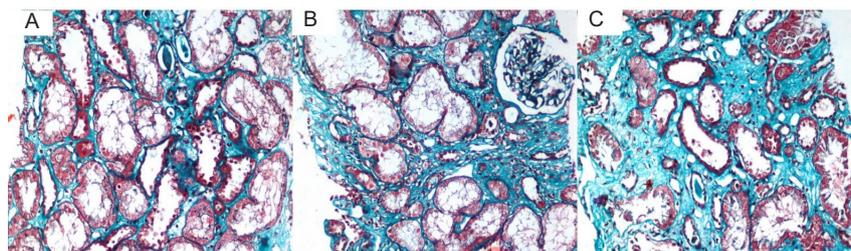
This study also showed that M1, T1 and T2 variables were accompanied by increased risk of kidney failure (28). A recent study in Paris by Cambier et al, on 129 adults and 82 children with IgAN showed higher ratio of mesangial proliferation and the presence of endocapillary hypercellularity in children compared to adults. On the other hand, focal segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis more than 25%, and podocytopathy, were more frequent in adults. This study showed proteinuria was associated with mesangial proliferation, endocapillary hypercellularity, and presence of crescents in pediatric cases; however, segmental glomerulosclerosis, podocytopathy, and interstitial fibrosis and tubular atrophy were more frequent in adults (29). Yu et al interestingly investigated a new sub-classification



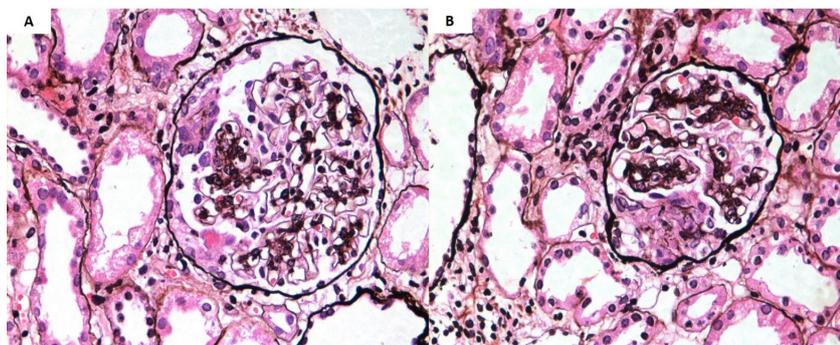
**Figure 2.** (A) One glomerulus from the renal biopsy of a patient with IgA nephropathy. It is showing segmental mesangial hypercellularity, as well as segmental endocapillary hypercellularity qualifying this biopsy as E1 according to Oxford classification. This lesion is reversible with immunosuppressive treatment, the later often masks its predictive value. (H&E,  $\times 200$ ) (B). High-power view of the same glomerulus showing segmental endocapillary hypercellularity with obliteration of capillary lumen at 11 to 12 O'clock position. Karyorrhectic debris is also present. Podocytes and parietal epithelial cells are prominent over this segment (H&E,  $\times 400$ ).



**Figure 3.** (A) One glomerulus from the renal biopsy of a patient with IgA nephropathy. It is showing segmental sclerosis of healed scar type, characterized by pale staining on PAS staining and wide attachment with Bowman's capsule. Presence of this lesion in even one glomerulus qualifies the biopsy as S1 according to Oxford classification. This is a chronic lesion involving the glomeruli in IgA nephropathy and a harbinger of progressive kidney damage (PAS,  $\times 400$ ). (B) Another glomerulus from a different biopsy of a patient with IgA nephropathy showing segmental sclerosis of podocytopathic nature. There is some prominence of podocytes at 7 to 8 O'clock position (PAS,  $\times 400$ ).



**Figure 4.** (A) Renal biopsy from a patient with IgA nephropathy showing mild tubular atrophy and interstitial fibrosis involving around 20% of the parenchyma in this particular field. This degree of tubular atrophy qualifies for T0 score according to Oxford classification. This is also chronic lesion involving the tubulointerstitial compartment in IgA nephropathy and is most reliable predictor of progressive kidney damage (Trichrome,  $\times 200$ ). (B) Another biopsy from a patient with IgA nephropathy showing moderate tubular atrophy and interstitial fibrosis involving around 40% of the parenchyma in this particular field. This degree of tubular atrophy qualifies for T1 score according to Oxford classification (Trichrome,  $\times 200$ ). (C) Another biopsy from a patient with IgA nephropathy showing severe tubular atrophy and interstitial fibrosis involving more than 50% of the parenchyma in this particular field and qualifying for T2 score according to Oxford classification. (Trichrome,  $\times 200$ ).



**Figure 5.** (A) One glomerulus from the renal biopsy of a patient with IgA nephropathy. It is showing fibrin accumulation in extracapillary space accompanied by proliferation of parietal epithelial cells in an early stage of crescent formation. The proportion of glomerular involvement is used to score crescentic (C) lesions in revised Oxford classification (JMS,  $\times 400$ ). (B) Another glomerulus from the same biopsy showing segmental crescent at 6 to 7 O'clock position. There is mild interstitial inflammation (JMS,  $\times 400$ ).

of segmental sclerosis scores of S0 (absence of S lesion), S1 (S lesion in less than 25% of glomeruli), and S2 (S lesion in more than 25% of glomeruli) in a review of the Oxford classification. They concluded that, the new sub-classification of segmental sclerosis scores may be beneficial in evaluating the pros and cons of immunotherapy in IgAN (30). El Karoui et al studied the significance of focal segmental glomerulosclerosis (FSGS)-like lesions in IgAN patients and concluded that these are associated with significantly poor renal survival at 80 months as compared to those without FSGS-like lesions. (31) Such lesions represent participation of at least three pathogenetic mechanisms which have different prognostic value. (32).

#### Significance of crescents in IgAN (MEST-C scores)

In the revised Oxford classification, crescents were included as a parameter of poor prognosis. Extra-capillary proliferation involving more than 50% of the glomeruli is frequently associated with rapid development of renal failure in IgAN patients (33). Patients with such

presentation of IgAN were excluded from the original Oxford classification study cohort. A recent single-center retrospective analysis by Neves et al, on biopsy-proven IgAN cases in 111 patients showed that crescent formation was associated with higher rate of hematuria, hypertension, and worse renal function with raised serum creatinine. The crescentic group also had higher number of individuals with endocapillary hypercellularity, segmental sclerosis and interstitial fibrosis and tubular atrophy. Moreover, the mean follow-up period was shorter in the group having crescents. In addition, the poor outcome (development of ESRD or doubling serum creatinine) was observed in a greater proportion of patients and in a shorter length of time in this group than in individuals without crescents. This study also showed that the other independent morphological risk factors for the development of ESRD or doubling serum creatinine were segmental sclerosis, interstitial fibrosis/tubular atrophy, and crescents (34). A study by Wang et al, on 100 IgAN individuals with different proportions of extra-capillary proliferation

showed that cases with more than 50% crescent formation had higher complement activation values than the other individuals. The results from this study showed that, complement hyper-activation may be involved in the development of extra-capillary proliferation, notably diffuse crescent formation, in these patients (33). More recently, volume of crescents was investigated by Lin et al, to evaluate the prognosis of IgAN in individuals without chronic morphologic lesions on renal biopsy (35). This study included 305 biopsy-proven IgAN patients. In their patients, 75.7% were in the no crescents (NC) group, 14.8% were in the segmental crescents (SC) group, and 9.5% were in the global crescents (GC) group. They found that compared with the NC group, patients in the SC group and the GC group had more proteinuria, lower eGFR, and more severe pathological changes. On multivariate analysis, the GC group was associated with an increased risk (HR = 2.756, 95% CI = 1.068– 7.109) of adverse outcome. They concluded that global crescents can be an independent risk factor for the development of progressive kidney failure in IgAN (35).

In summary, Oxford classification of IgAN has proved to be an independent and earlier risk stratification parameter for patients with IgAN and when combined with clinical and laboratory features at the time of diagnosis, it can achieve accurate risk assessment two years earlier than methods used in current clinical practice.

### Conclusion

In conclusion, the risk stratification and prognostication of IgAN has markedly improved the use of the Oxford classification of IgAN. Clinicians should take into account the pathologic variables according to the revised Oxford classification in addition to established clinical and laboratory parameters for early, accurate and reliable prognostication in individual patients at the time of diagnosis in IgAN.

### Authors' contribution

Conceptualization: DJ and RT. Methodology: RT. Validation: LAH and MM. Formal Analysis: MM. Investigation: JB and LM. Data Curation: MM. Writing—Original Draft Preparation: DJ, MM and RT. Writing—Review and Editing: TS and JB. Visualization: MM. Supervision: MM and RT. Project Administration: RT.

### Conflicts of interest

The authors declare no conflicts of interest.

### Ethical issues

The authors have entirely observed ethical issues (including plagiarism, data fabrication, and double publication).

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