

Oxford Classification of IgA Nephropathy 2016

An update from the IgA Nephropathy Classification Working Group

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Abstract

Since the Oxford Classification of IgA nephropathy (IgAN) was published in 2009, MEST scores have been increasingly used in clinical practice. Further retrospective cohort studies have confirmed that in biopsies with a minimum of 8 glomeruli M, S and T lesions predict clinical outcome. In a larger broader based cohort than in the original Oxford study, crescents (C) are predictive of outcome, and we now recommend that C is added to the MEST score, and biopsy reporting should provide a MEST-C score. Inconsistencies in the reporting of M and E lesions have been reported, so a web-based educational tool to assist pathologists has been developed. A large study showed E lesions are predictive of outcome in children and adults but only in those who without immunosuppression. A review of S lesions suggests there may be clinical utility in the sub-classification of segmental sclerosis, identifying those cases with evidence of podocyte damage. It has now been shown that combining the MEST score with clinical data at biopsy provides the same predictive power as monitoring clinical data for two years; this requires further evaluation to assess earlier effective treatment intervention. The IgAN Classification Working Group has established a well characterized dataset from a large cohort of adults and children with IgAN which will provide a substrate for further studies to refine risk prediction and clinical utility, including the MEST-C score and other factors.

Key words: IgA nephropathy; proteinuria; chronic kidney disease; glomerulonephritis

Introduction

The Oxford Classification of IgA nephropathy was first published in 2009 following a five year effort by a working group of nephrologists and renal pathologists representing the International IgA Nephropathy Network and The Renal Pathology Society^{1,2}. The classification was based on objective evidence developed in a cohort of 265 adults and children of European Caucasian and East Asian ethnicity with IgAN. The classification indicated that there were only three reproducible variables seen in the renal biopsy in IgAN that independently predicted outcome and provided prognostic information added to prognosis prediction given by clinical features alone. The three features were mesangial hypercellularity (M), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T). In addition, among patients with endocapillary hypercellularity (E) the rate of renal functional decline was significantly lower in those receiving immunosuppressive therapy. The Oxford Classification thus includes these four parameters, the MEST scores.

Since 2009 the classification has been widely adopted in clinical practice, largely replacing other previously popular classifications which were not fully evidence-based. A number of studies have sought to validate the predictive value of MEST in other more inclusive retrospective cohorts. This has included demonstrating the value of the Oxford classification predicting long-term outcomes of Henoch-Schönlein purpura nephritis (IgA vasculitis) as well as IgAN³, although data are not yet sufficient to make a recommendation that the MEST score should be used routinely in IgA vasculitis

Other studies have investigated features not predictive of outcome in the original Oxford study, most notably patterns of immunofluorescence staining for IgA and complement components, and glomerular crescents⁴. Studies have also sought to develop more precise approaches to the combination of clinical features with the MEST score to improve prognostic accuracy. The original working group, with some changes in membership,

continues to be active, has held further meetings including another in Oxford in 2014, and has established subgroups that focus on individual unanswered questions.

In this report we review the relevant studies published since 2009, as well as reporting the published and yet unpublished studies of our working subgroups. We make recommendations for changes to the Oxford Classification, and also propose further work which will improve still further the value of the classification in research and in clinical practice.

Published retrospective validation studies

A limitation of the original Oxford study cohort was that it included only 265 adults and children, and only those of White Caucasian (from Europe and North America) and East Asian (from China and Japan) ethnicities. Furthermore, the cohort was selected to be enriched for typical slowly progressive IgAN, excluding patients with very low levels of proteinuria. It also excluded those with estimated GFR <30ml/min with the intent of avoiding the selection of very advanced cases in which glomerulosclerosis and interstitial fibrosis would be dominant, but having the effect of also excluding some rapidly progressive cases in which crescents might more likely be predictive of outcome.

Since 2009, numerous studies have been published which apply the Oxford classification to cohorts of subjects with IgAN. These studies are typically described as validation studies, although none prospectively studied new cohorts; nevertheless they provide valuable corroborative evidence. Sixteen such studies⁵⁻²⁰, including cohorts from Europe, North America, and East Asia were meta-analysed in a report published in 2013²¹. Lately, more studies have been published including cohorts from Iran, Europe, Japan and Korea²²⁻²⁸. All these studies are summarised in Supplementary Table 1.

Review of current classification parameters (M, E, S, and T)

The published cohorts provide robust and consistent evidence that M, S and T lesions each reliably provide prognostic information by univariate analysis, although only T lesions were a consistent, independent predictor of renal outcomes, with more variable results for M and S (Table 1). This is likely to be a consequence of the endpoint (end stage renal disease, ESRD) chosen in most studies. T score largely reflects the stage of disease at the time of biopsy; those patients with more advanced chronic damage have a shorter time to ESRD. Those studies that included rate of loss of renal function as an endpoint, more consistently reported that active, cellular lesions (M and E score) were associated with this outcome.

E (endocapillary hypercellularity)

The E lesion was not predictive of outcomes in the original Oxford Classification cohort, and this was also true in most of the subsequent studies (Table 1). However, the original Oxford Classification cohort and all but two of the published validation studies show treatment bias, with non-random immunosuppression. Patients whose biopsies were scored E1 were more likely to receive immunosuppressive therapy, most frequently corticosteroids, and patients with E lesions had an improved outcome if treated with corticosteroids. The two studies in which no patients received corticosteroid/cytotoxic therapy both reported that E1 was independently associated with more rapid loss of renal function and worse renal survival^{8,27}. This is consistent with the reversibility of E following immunosuppression in a study reporting repeat renal biopsies after treatment²⁹. These studies suggest that the use of immunosuppression may mask the predictive value of E on renal outcomes. While these findings do not in themselves support the routine use of immunosuppression when the E lesion is present, they do justify a prospective trial of immunosuppression in IgAN with the E lesion.

S (Segmental sclerosis)

Segmental sclerosis may develop as a consequence of distinct processes. It might result from organisation of segmental necrotising or endocapillary inflammatory lesions. Alternatively, it may reflect a response to podocyte injury (podocytopathy) analogous to primary FSGS. The underlying cause of the sclerosis might be associated with different histological features within the segmental sclerosing lesions. A recent publication reviewed segmental sclerosing lesions in the Oxford Classification patient cohort and correlated histology with clinical presentation and outcome³⁰. This showed that podocyte hypertrophy or sclerosis at the tubular pole (tip lesion), features typically associated with podocytopathies, were associated with more proteinuria at presentation and a more rapid decline in renal function. In addition, in individuals with podocyte hypertrophy or tip lesions, immunosuppressive therapy was associated with a better renal survival. The identification of these podocytopathic features was found to be reproducible between the pathologists in the study but it remains to be determined whether this is also the case for pathologists in different units around the world. If the associations between histological subclassification of segmental sclerosis and outcome are confirmed, then a refinement of the definition of the S lesion may be appropriate, using S1 only for sclerotic lesions with podocytopathic features. Pending such studies we recommend no change in the definition of S1, but reporting all S1 lesions with additional descriptive text “segmental sclerosis with/without podocyte hypertrophy/tip lesions”.

Additional pathological features considered for inclusion in the Oxford Classification

Pattern of glomerular IgA deposition

The Oxford Classification was developed using light microscopic findings only. Other reports have suggested that the presence of IgG, in addition to IgA, and also the location of IgA are predictive of outcome, for example that glomerular capillary wall deposits may carry

a worse prognosis than mesangial deposits alone⁴. However, review of the Oxford Classification cohort has shown that whilst the presence of glomerular IgG and capillary wall IgA deposits (identified by immunofluorescence or immunohistochemistry) are associated with a worse outcome, they do not add predictive value to MEST scores⁴.

Crescents

In the original Oxford study¹ and several validation studies with similarly restrictive entry criteria^{7,9,15,16}, crescents were not found to be an independent predictor of renal outcomes. However individuals with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 ml/min) were not included in these studies, and Katafuchi et al found crescents to be predictive of end stage renal disease in 286 IgAN patients not meeting entry criteria for the original Oxford study⁶. Crescents were also found to be predictive of poor renal outcomes in several other studies including patients with eGFR <30 ml/min^{12,13}. A working subgroup of the IgAN Classification Working Group has addressed crescents as a potential predictor of renal outcomes in IgAN in a pooled cohort of 3096 patients assembled from 4 retrospective studies³¹: Oxford^{1,2}, VALIGA²³ and 2 large Asian databases, one from China¹⁷ and another from Japan⁶. The working subgroup studied relationships between the proportion of glomeruli containing cellular or fibrocellular crescents and the rate of renal function decline and survival from a 50% decline in renal function or end stage renal disease (combined event), while adjusting for covariates used in the original Oxford study.

In this combined cohort (including biopsies with a minimum of eight glomeruli, as required for a MEST score) the presence of crescents was strongly associated with subsequent use of immunosuppression. Overall, crescents were independently predictive of a higher risk of a combined event (hazard ratio 1.37, 95% CI 1.07-1.75). This association remained statistically significant only in those patients who did not receive immunosuppression. There was also a proportion-dependent relationship between the

fraction of crescents and outcomes: in individuals with crescents in $\geq 1/6$ and $\geq 1/4$ of glomeruli, the hazard ratio of a combined event rose to 1.63 (95% CI 1.10-2.43) and 2.29 (1.35- 3.91), respectively. Interestingly, the risk of a combined outcome associated with crescents in $>25\%$ of glomeruli remained significant in patients receiving immunosuppression as well as those who were not.

The findings of this working group support the addition of crescent scores (C0, C1, and C2) to the Oxford MEST scores. A score of C1 (crescents in $<25\%$ of glomeruli) versus C0 (no crescents) identifies a group of patients having a significantly higher risk of a poor renal outcome than patients whose biopsies had no crescents (C0 score) if not treated with immunosuppression, but not if treated with immunosuppressive therapy. The findings with C1 are similar to those found in the original Oxford¹ and validation⁷ cohorts for E1, however as with the latter these observational data are not sufficient to extrapolate to a recommendation that those with C1 lesions should be treated with immunosuppression. A score of C2 (with crescents in $>25\%$ of glomeruli) further identifies patients at risk of a poor renal outcome even if treated with immunosuppression³¹. Therefore, we propose that the Oxford classification should now involve five components, MEST-C rather than MEST. Cases of Henoch-Schönlein purpura nephritis were not included in this cohort, so it is not yet possible to confirm whether crescents have similar significance in that condition.

Quantification of glomerular macrophages

It has been proposed that E1 in IgAN is a reflection of glomerular inflammation and that use of immunohistochemistry for CD68 to identify glomerular macrophages might assist in the recognition of E1 lesions, and be potentially superior to evaluation of PAS-stained sections in prognostication. There is provisional data from the study of biopsies in a cohort which received no immunosuppression, and in which E1 was an independent predictor of rate of loss of renal function and renal survival²⁷. In these biopsies quantitative analysis of CD68-

stained sections has demonstrated that the number of glomerular macrophages correlates strongly with extent of endocapillary hypercellularity and E1 score, assessed on PAS-stained sections, but not M, S or T scores. Using a cut-off of a maximum glomerular macrophage count of 6 correctly identifies E score in 80% of biopsies³². It remains to be determined whether glomerular macrophage counts have superior clinical value to E scoring.

Children

The validation studies in children <18 years old from Japan¹³, China¹⁶, Sweden¹² and VALIGA²³, confirmed the value of the MEST scores by univariate analysis. However, by multivariate analysis no individual feature maintained an independent predictive value, apart from T lesions in pediatric Chinese patients. This was likely due to the limited number of patients reaching end points. In young subjects aged <23 years enrolled in VALIGA the MST variables were predictive by multivariate analysis for survival from a combined end point of 50% decline in renal function or end stage renal disease³³. In other cohorts, significant predictive values for some scores (mostly M, E and T) were found in models including clinical data at renal biopsy. The most powerful predictive factor in children and young subjects, using Cox models as well as tree analysis, is M1. In the Japanese cohort the presence of crescents in >30% glomeruli was also significant in multivariate models considering proteinuria at biopsy¹³. These analyses stress the need for a collaborative effort to generate a large database for children with IgAN in order to solve the problem of inadequate statistical power due to small numbers of progressive cases especially with relatively short periods of follow-up.

Combined clinicopathological information

The major aims of our work in developing and refining a classification of IgAN are to improve the prognostic information for individual patients and recruitment criteria into clinical trials. Earlier prediction algorithms sought to integrate clinical findings at

presentation and over time with renal pathology using the histological classifications for IgAN available at the time³⁴. By univariate analysis many clinical and pathological elements were relevant to outcomes but by multivariate analysis the only factors which maintained their independent value were mean arterial pressure and urine protein excretion over time³⁴. Maximum predictive power to explain variabilities in outcome in any patient, was only available when mean arterial pressure and proteinuria were followed for a two-year period. Recently, this was explored further using a combined cohort of 901 adults from the original Oxford cohort, the North American validation study and the VALIGA study. The previous prediction algorithm, using clinical data (including proteinuria, mean arterial function and glomerular filtration rate) over the first 2 years was repeated using the hard endpoints of a 50% decrease in estimated glomerular filtration rate or end stage renal disease and with current prediction model statistical approaches. The predictive power of that original algorithm was then compared to the predictive power of the MEST scores alone and to the addition of MEST scores to the initial clinical data at time of biopsy. There was significant improvement in prediction by adding MEST to clinical data at biopsy and predicted outcome and the two-year clinical data alone, with comparable calibration curves. This effect did not change with further analyses of those who were and were not treated with renin angiotensin system blockade or immunosuppression. The impact on outcome of individual elements of the MEST score was analysed. Mesangial hypercellularity decreased the likelihood of renal survival from 90% (M0) to <80% (M1) at 5 years in patients with the same clinical parameters³⁵. Further prospective studies are needed to establish whether this combination of clinical and pathological information at the time of biopsy would allow earlier introduction of therapy with better long-term preservation of renal function.

Other prediction models for outcome in IgAN have been published³⁵ using a variety of pathological features and clinical features. Our working group will continue to refine these

prediction models using the MEST-C score and will seek international consensus so that one prediction model enters common usage. This will not only benefit individual patient care but will also facilitate collaborative research, and enable comparison and interpretation of different studies.

The Revised MEST-C Score

Criteria for adequacy of renal biopsy, for scoring of M, E, and T lesions, and for overall reporting of IgAN biopsies are unchanged from our original recommendations^{1,2} (Boxes 1 & 2). In light of the recent data summarised above, we recommend the addition of a C (crescent score) to MEST. All adequate biopsies with a diagnosis of IgAN should be scored as C0 (no crescents), C1 (crescents in a least one but <25% of glomeruli) or C2 (crescents in at least 25% of glomeruli) (Boxes 1 & 2). We also recommend refining the S score, noting the presence or absence of podocytopathic features (podocyte hypertrophy/tip lesions) in biopsies scored as S1.

Therefore, we propose that the renal biopsy in IgAN should be reported using a five-component MEST-C score. Since cases of Henoch-Schönlein purpura nephritis were excluded from the recent study of crescents in IgAN³¹, we recommend the MEST-C score not to be applied to cases of Henoch-Schönlein purpura nephritis yet.

Reproducible identification of MEST: need for an educational tool

The definitions for each component in the Oxford Classification were the result of an iterative process involving the renal pathologists in the original working group². Definitions were written to be straightforward and to maximise the likelihood that pathologists would be able to consistently identify the lesions in clinical practice. However, a subsequent analysis using the VALIGA cohort showed significant inconsistencies in identification of M and E lesions³³. Local pathologists diagnosed M1 twice as often as the central review pathologist and E1 three times as often. The M score given by the central but not the local pathologists

was an independent predictor of renal outcome. To help overcome this issue a web-based tool has been developed to provide examples of each lesion and assist pathologists to overcome the commonly identified reporting errors. The link to training slides will soon be available on the Renal Pathology Society website (www.renalpathsoc.org).

Next Steps

Development of international cohorts for further studies

A key achievement of the original Oxford Classification working group was the assembly of a study cohort of sufficient size with detailed clinical and pathological data that allowed us to address the questions posed. The international collaborative effort which led to the original Oxford Classification continues and we are currently assembling a cohort from multiple centres across Europe, China, Japan, North and South America. The objective is to develop a cohort representing the full spectrum of disease severity in IgAN with no limitations on proteinuria or renal function. This cohort will be representative of a wide-range of ancestries, countries, patterns of practice and age, and is characterized by deep patient level clinical phenotyping, consistent data collection and detailed histologic long follow-up analysis to enable address novel questions that are not possible using smaller local datasets. Approximately 5000 such patient datasets including children and adults have been collected and preliminary analysis has been published³⁶. This cohort will be a powerful substrate for further studies in IgAN to improve outcome prediction for individual patients, and refine recruitment and outcome criteria for clinical trials. The primary purpose will be to validate a prediction model in IgAN applicable worldwide across the range of disease severity and ethnic groups, and easy to use in clinical practice (analogous to the Framingham prediction rule for cardiovascular disease). In addition, we expect this cohort be a data source for further studies including the potential for virtual assessment of novel biomarkers.

Biomarkers

An important research focus in IgAN is the identification of novel biomarkers which can add to the available information through clinical and pathological features improving diagnosis, risk stratification, therapy selection, prediction of response to therapy, and risk of transplant recurrence. With the continued evolution of “omics” platforms it is now possible to measure a very wide range of potential ‘biomarkers’ in the serum, plasma, urine, and kidney. However, in IgAN there are few such biomarker studies and they lack rigorous prospective validation in diverse populations³⁷. Variable collection and storage of biological samples for biomarker analysis can be a significant confounder in such analyses. Undergalactosylated serum IgA1 and circulating autoantibodies to that IgA1 have been studied and may add value in predicting progression risk and transplant recurrence³⁸. Biomarkers have the potential to improve prediction of end stage renal disease, to assist the clinician in managing individual patients, and to define surrogate end points for the evaluation of clinical trials. To maximize the opportunity being created by the described large international IgAN cohort, recommendations will be agreed and published covering the collection, storage, and transport of biological specimens for biomarker analysis.

Discussion

The active study of the Oxford Classification of IgAN since its original publication has led to the assembly of substantial data to endorse its validity in increasingly large and diverse cohorts of patients. This progress provides further assurance that it was correct to develop the Oxford Classification using a rigorous evidence-based approach, which sets it apart from other, largely opinion-based, classifications currently used in renal pathology.

The Oxford Classification has now become the accepted norm used by the majority of clinicians and investigators worldwide. Nevertheless, there are challenges in its use. Although intended to be straightforward to use in everyday clinical practice because it provided simple and reproducible descriptions of each of its elements, evidence indicates that there is

inconsistent reporting of the M lesion, and particularly the E lesion. To improve the accuracy of MEST reporting an on-line educational program has been developed (www.renalpathsoc.org).

Another approach to improving the accuracy of E lesion reporting is to develop an additional cellular marker for endocapillary hypercellularity. Identification of tissue macrophages by CD68 staining is a promising approach which improved accurate identification of the E1 lesion in one study³⁹, but corroboration is needed before recommendation for inclusion in the Oxford Classification.

Recent data have clarified the prognostic significance of the E lesion. E1 is predictive of outcome only in patients who have not received immunosuppression. This strongly suggests the E lesion is responsive to immunosuppression, an interpretation supported by evidence from a re-biopsy study showing resolution of E lesions following immunosuppression²⁹. However, there are very few supporting data for this proposition from randomised clinical trials. Further histological data from controlled trials is required to determine the role of the MEST score and selection of therapy.

It has always been intended that the Oxford Classification would be subject to review and development, not least because of the rather narrow inclusion criteria used to assemble the original Oxford cohort of only 265 subjects. The original cohort was enriched with slowly progressive IgAN cases, thus maximising the chance of identifying significant associations of pathological features and outcome in such a small cohort. Further data from the many validation studies summarised here and elsewhere²¹⁻²⁶ endorse the continued use of the MEST score. These data also provide evidence of the predictive value of a C score. A C1 score (crescents in <25% of glomeruli) identifies those at risk of a poor renal outcome if not treated with immunosuppression; a C2 score (crescents in >25% of glomeruli) further identifies patients at risk of a poor renal outcome even if treated with immunosuppression³¹.

Immunosuppressive therapy is often used when crescents are identified in IgAN, although the evidence to support this approach is only anecdotal. While it is still premature to regard our observations as justifying the use of immunosuppression when C1 lesions are found, this should be investigated further in randomized clinical trials to determine if specific treatment recommendations should be made.

Another valuable role for the MEST-C score could be in interpreting repeat renal biopsies in IgAN. There are currently very few data on MEST scores in repeat biopsies so no recommendations can presently be made, although in the study of Shen et al²⁹ the fraction of patients with biopsies showing E1 lesions and crescents (but not M1 and S1 lesions) prior to immunosuppressive treatment decreased significantly on post-treatment biopsies.

A significant additional benefit of the development of the Oxford Classification for IgAN has been the building of an international network of investigators willing to work together, to sharing data and biosamples, to deliver collaborative projects not attainable by each investigator working with smaller cohorts. This network has now assembled a cohort of over 5000 subjects with detailed consistently held data on demographics, clinical phenotyping, and outcome, expecting to provide the substrate for future studies including analysis of novel biomarkers. Limited numbers provide a challenge to the study of IgAN in children; this cohort addresses this issue by including over 1000 children.

In summary, we propose an extension of the MEST score in the Oxford Classification of IgAN to become a MEST-C score for use in routine clinical practice and research. In addition to providing the evidence base to endorse this recommendation, the continuing efforts of our group have built a network to facilitate the assembly of a large unique cohort of well-characterised subjects with IgAN, providing fertile ground for further collaborative international studies addressing the pathogenesis, epidemiology, and clinical care of IgAN patients.

Disclosure

Hernán Trimarchi: Genzyme-Sanofi, Alexion
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Authorship

Hernán Trimarchi: Drafted the manuscript. Interacted with all authors and integrated opinions in the manuscript. Provided data, revised the manuscript and approved the final version.

Jonatan Barratt: Provided data and discussed results. Revised manuscript. Approved the final version.

Daniel Cattran: Conceived and/or designed the work that led to the submission, acquired data, and/ or played an important role in interpreting the results. Drafted or revised the manuscript. Approved the final version.

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Rosanna Coppo: Provided data, and/or played an important role in interpreting the results. Drafted or revised the manuscript. Approved the final version.

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Yusuke Yuzawa: Provided data. Approved the final data.

Hong Zhang: Provided data. Approved the final data.

John Feehally: conceived the work that led to this report; he drafted and revised the manuscript. Approved the final version.

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BOX 1:

Recommendations for updating the Oxford Classification of IgAN

- ☐ We recommend no changes to the published criteria for biopsy adequacy in cases of IgAN. A minimum of 8 glomeruli are required.

- ☐ We recommend that MEST criteria continue to be applied to cases of IgAN

- ☐ We confirm the predictive value of M,S and T

- ☐ We confirm the predictive value of E in patients not treated with immunosuppression

- ☐ We recommend that a C score be added to the MEST score in all cases of IgAN to indicate the frequency of cellular and/or fibrocellular crescents
 - C0 (no crescents) *or*
 - C1 (crescent in a least one glomerulus) *or*
 - C2 (crescents in at least 25% of glomeruli)

- ☐ We recommend no change in the definition of S1, but adding text to indicate whether or not there are podocytopathic features

☐ We recommend that MEST criteria are not yet applied to cases of Henoch-Schönlein purpura nephritis (IgA vasculitis)

BOX 2:

Recommendations for the renal biopsy report in IgA nephropathy

Updated from ref. ^{1,2,33}

Detailed description of the features present on

Light microscopy

Immunohistochemistry or immunofluorescence

Electron microscopy

Summary of five key pathological features

Mesangial score < 0.5 (M0) or >0.5 (M1)

Endocapillary hypercellularity absent (E0) or present (E1)

Segmental glomerulosclerosis absent (S0) or present (S1); presence or absence of podocyte hypertrophy/tip lesions in biopsies with S1

Tubular atrophy/interstitial fibrosis ≤25% (T0), 26-50% (T1), or >50% (T2)

Cellular/fibrocellular crescents absent (C0), present in at least one glomerulus (C1), in ≥25% of glomeruli (C2)

Quantitative data

Total number of glomeruli

Number of glomeruli with endocapillary hypercellularity, necrosis, extracapillary hypercellularity (cellular/fibrocellular crescents), global glomerulosclerosis and segmental glomerulosclerosis

Table 1. Summary of Studies Correlating Oxford MEST Parameters with Clinical Outcomes in IgA Nephropathy

Minimum cohort size - 99 patients

STUDY AND COUNTRY	CENTRE	NUMBER OF PATIENTS	ENDPOINT	UNIVARIATE ANALYSIS	MULTIVARIATE ANALYSIS	IS BIAS
Cattran et al¹ (Oxford) 2009	Multicentre global	265 (206 A, 59 C)	Rate eGFR decline ESRD or $\geq 50\%$ eGFR decline	M,S,T M,S,T	S,T M,T	Yes
Katafuchi et al⁶ 2011	Single centre Japan	702 C	ESRD	MET	MET	Yes
Herzenberg et al⁷ 2011	Multicentre USA & Canada	187 (143 A, 44 C)	Rate eGFR decline	Not done	E,S,T	Yes
El Karoui et al⁸ 2011	Single centre France	128 A	ESRD or doubling of SCr Rate eGFR decline	NONE	M,E,S,T	No
Shi et al⁹ 2011	Single centre China	410	ESRD	M,S,T	S,T	Yes
Alamartine et al¹⁰ 2011	Single centre France	183	ESRD or doubling of Scr	E,S,T	NONE	Yes
Edstrom Halling¹² et al 2012	Single centre Sweden	99 C	ESRD or $\geq 50\%$ eGFR decline	M,E,T	NONE	Yes
Shima et al¹³ 2012	Single centre Japan	161 C	Rate eGFR decline	M,E,T	M,T	Yes
Le et al¹⁵ 2012	Multicentre China	218 C	eGFR decline (doubling Scr) or ESRD	S,T S,T	T T	Yes
Zeng et al¹⁷ 2012	Multicentre China	1026 A	Rate eGFR decline ESRD or $\geq 50\%$ eGFR decline	M,S,T M,S,T	M,T M,T	Yes
Kang et al¹⁸ 2012	Single centre Korea	197 A	ESRD or $\geq 50\%$ eGFR decline	T	T	Yes

Gutierrez et al²⁰ 2012	Single centre Spain	141 A	eGFR decline (doubling Scr) ESRD	T S	T S	Yes
Nasri et al²² 2012	Multicentre Iran	102 A	Scr	ST	Not done	Yes
Coppo et al²³ 2014 VALIGA	Multicentre Europe	1147 (973 A, 174 C)	ESRD or $\geq 50\%$ eGFR decline Rate eGFR decline	M,S,T M,S,T	S,T S,T	Yes
Espinosa et al²⁴ 2014	Multicentre Spain	283 (A + C)	ESRD	M,S,T	S,T	Yes
Moriyama et al²⁵ 2014	Single centre Japan	1012 A	eGFR decline or ESRD	T	NONE	Yes
Park et al²⁶ 2014	Multicentre Korea	500 A	ESRD or doubling of Scr	M,T	T	Yes
Chakera et al²⁷ 2016	Multicentre Australia, UK	156 A	ESRD or eGFR decline > 5ml/min/year	E,T	E	No
Hou et al²⁸ 2016	Multicentre China	176 A	Proteinuria	Not done	Not done	Yes

Abbreviations: IS, immunosuppression; IS bias, inherent bias due to non-randomized use of immunosuppressive therapy in study cohort; A, adults; C, children; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; ESRD, end-stage renal disease; M, mesangial proliferation; E, endocapillary proliferation; S, glomerulosclerosis; T, tubular atrophy.