The Correlation Analysis between the Oxford Classification of Chinese IgA Nephropathy Children and Renal Outcome - A retrospective cohort study

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Abstract

Background: The 2016 Oxford Classification's MEST-C scoring system predicts outcomes in adults with IgA nephropathy, but it lacks large cohort validation in children with IgAN in China. We sought to verify that the MEST-C score can be used to predict the renal outcome of children with IgAN.

Methods: A retrospective cohort analysis of data from 1243 Chinese children with IgAN who underwent renal biopsy in Jinling Hospital from January 2000 to December 2017. We studied the relationship between the Oxford Classification and renal outcome [a combined renal endpoint: 50% estimated glomerular filtration rate (eGFR) loss or end-stage renal disease (ESRD)].

Results: There were 29% of patients with mesangial proliferation (M1), 35% with endocapillary proliferation (E1), 37% with segmental sclerosis/adhesion lesion (S1), 23% with moderate tubulointerstitial fibrosis (T1 26-50% of cortex scarred), 4.3% with severe tubulointerstitial fibrosis (T2, >50% of cortex scarred), 44% with crescent in <25% of glomeruli (C1), and 4.6% with crescent in >25% of glomeruli (C2). During a median follow-up duration of 86.8 months, 171 children (14%) developed ESRD or 50% decline in renal function. An early diagnosis seems to be the major reason for a low frequency of chronic and severe lesions such as S, T and C lesions. In the multivariate Cox regression model, Only S (HR 2.7, 95% CI, 1.8-4.2, P < 0.001) and T lesions (HR 6.6, 95% CI, 3.9-11.3, P < 0.001) were associated with the rate of eGFR loss in the whole cohort, whereas C lesion showed this association only in patients not treated with immunosuppression.

Conclusions: We found that S and T lesions were valid in predicting a renal outcome in Chinese IgAN Children.

Introduction

IgA nephropathy (IgAN) is the most frequent primary glomerular disease worldwide and the main cause of end-stage renal disease (ESRD) in patients of all ages [1]. Since IgAN does not exhibit a specific serologic profile, a percutaneous kidney biopsy remains the definitive tool to establish the diagnosis of IgAN [2]. Additionally, the prognostic value of histological data has become increasingly recognized in the past decade [3]. As a new pathological classification standard to judge the renal prognosis of IgAN, the Oxford classification [4] have been put forward in recent years. The purpose of
the Oxford classification is to consider the pathological features associated with clinical outcomes independently of clinical data and to improve the current ability to predict outcomes in IgAN patients. Although the classification standard has been formulated by rigorous methodology, its clinical application in children needs to be further verified. What’s more, IgAN has regional and ethnic differences, which determines that the Oxford classification needs to be refined in different populations and races. In this study, the clinical and pathological data of IgAN patients followed up for a long time in our department were retrospectively analyzed to assess the predictability of Oxford classification among Chinese IgAN children.

Materials And Methods

1. Patients

The protocol followed in the present study was approved by the Jinling Hospital Ethics Committee on Human Experimentation. The clinical and pathological data of 1243 children with primary IgAN diagnosed by renal biopsy in Jinling Hospital from January 2000 to December 2017 were collected. The diagnosis of IgAN was based on the presence of IgA as the sole or predominant immunoglobulin in the glomerular mesangium in the absence of systemic disease. Patients with the secondary IgAN caused by Henoch-Schonlein purpura, diabetes mellitus, liver cirrhosis, systemic lupus erythematosus, hepatitis B virus infection, tumor, ankylosing spondylitis and psoriasis were excluded. Patients with a follow-up duration of <12 months were excluded.

2. Clinical data and definitions

The following data were collected at baseline: age, gender, duration from onset to renal biopsy, estimate glomerular filtration rate (eGFR), mean arterial pressure (MAP) and urine proteinuria (UP). eGFR was calculated using the Schwartz formula[5], and the CKD-EPI equation[6] was used in patients aged >16 years at the time of biopsy. MAP was calculated from systolic blood pressure (SBP) and diastolic blood pressure (DBP) (MBP = 1/3 × (SBP–DBP) + DBP). Survival time was defined from baseline (kidney biopsy) until the date of the last follow-up, the incidence of the event of interest, or December 31, 2018 (end of the study). End-stage of renal disease (ESRD) was defined as eGFR <15 mL/min/1.73m², initiation of dialysis or transplantation. A combined event was defined as ESRD or
50% reduction in initial eGFR. Renin angiotensin aldosterone system blockade (RASB)/glucocorticoid /other immunosuppressant treatment was evaluated on an intent-to-treat basis, regardless of the type or duration of therapy.

3. Pathology review

Renal pathology were scored according to the Oxford Classification[4], including mesangial hypercellularity(M), endocapillary hypercellularity(E), segmental sclerosis(S), interstitial fibrosis/tubular atrophy(T) and cellular/fibrocellular crescents(C). The pathology classification was performed as follows: M0 indicated a mesangial score ≤0.5, or ≤50% of glomeruli with ≥4 mesangial cells per mesangial area, M1 indicated a mesangial score > 0.5, or > 50% of glomeruli with ≥4 mesangial cells per mesangial area. E0 or E1 indicated the presence or absence of endocapillary hypercellularity, respectively. S0 or S1 indicated the presence or absence of segmental sclerosis or tuft adhesions, respectively. T0, T1, and T2 indicated the degree of tubular atrophy or interstitial fibrosis (< 25%, 25–50%, and >50%, respectively) C0, C1 and C2 indicated no crescent in glomeruli, crescent in < 25% of glomeruli, and crescent in >25% of glomeruli, respectively.

Immunofluorescence studies were performed (IgG, IgA, IgM, C3) and showed at least 1+(on scale from 0 to 4+) mesangial deposition of IgA, with IgA being the dominant immunoglobulin deposited in the glomeruli. At least two pathologists blinded to patient outcomes at the time of review confirmed the pathological results.

4. Statistical analyses

Data were analyzed with the SPSS (version 24.0, SPSS Inc, Chicago, IL). Normally distributed data were expressed as the mean ± standard deviation (SD), and non-parametric data were expressed as the median and interquartile range. Continuous data were compared using the Mann–Whitney U test, and categorical data were compared using Fisher’s exact test. Cumulative event rates were calculated using the Kaplan–Meier method. The Cox proportional hazard model was used to identify prognostic factors for combined event. All P values were two-tailed, and P values of <0.05 were considered to be statistically significant.

Results
1. Clinical Findings

Clinical findings were shown in Table 1. The 1243 children had initial eGFR of 102±20 ml/min/1.73m². The cohort was 32% female and all were Chinese Han children. The initial UP was 1.0 (0.5–2.4) g/d. Patients were followed for a median of 86.8(54.7–140.2) months, during which 45% received CS and 70% received RASB. MAP was 89±16mmHg, 14% experienced a combined event (ESRD or 50% reduction in initial eGFR), and 6.6% experienced ESRD. During the follow-up, 70% of patients were treated with RASB and 45% with corticosteroids and 19% were treated with corticosteroids combined other immunosuppressive drugs.

2. Pathological Findings

Pathological findings were shown in Table 2. According to Oxford classification, 29% of the children showed M1, 35% showed E1, 37% showed S1, 23% showed T1, 4.3% showed T2, 44% showed C1 and 4.6% showed C2. The distribution of the percentage of crescents observed in every children was shown in Figure 1. 28% had crescents in 10% of glomeruli, 9.4% had a fraction of glomeruli with crescents one tenth or more, whereas 6.6% had a fraction of glomeruli with crescents one sixth or more, and only 4.6% had a fraction of glomeruli with crescents one fourth or more. The percentage of immunoglobulins deposited only in the mesangial region was 68%, while 32% of immunoglobulins were deposited in both the mesangial and capillary loop regions. 25% Children showed positive glomerular staining for IgG, 44% showed positive glomerular staining for IgM, 84% Children showed positive glomerular staining for C3, and 1.1% Children showed positive glomerular staining for C4. The immunofluorescence intensity of IgA was between ++ and ++++, including 5.6% of ++, 13% of +++ and 81% of ++++. 

3. Effects of Different Kidney Biopsy Time on the Variables in Oxford Classification

We selected the median time (12 months) of onset to renal biopsy as the cut-off point to analyze the effect of biopsy time on variables in the Oxford classification. From Table 3, we can see that when the median time of onset to renal biopsy was less than the median time, the patient's lesions were milder, dominated by S0 (c2=354.5, P<0.001), T0 (c2=323.3, P<0.001), and C0 (c2=437.6, P<0.001). On the
contrary, when the time of renal biopsy was longer than the median time, the lesions were corrected
mainly by S1, T1-2 and C1-2. With regard to E and M lesions, there was no significant difference in time
from onset to renal biopsy within available data.

4. Relationship between Oxford Classification and Clinical Indicators

In order to study the correlation between Oxford classification and clinical indicators, three clinical
indicators of MAP, eGFR, UP, which are closely related to renal prognosis, were selected for
preliminary simple linear regression analysis. Correlations between pathological variables and clinical
presentation at biopsy were shown in Table 4. M1, E1, T1-2 and C1-2 were associated with MAP at
biopsy. S1, T1-2 and C1-2 were associated with eGFR at biopsy. All pathological variables were
associated with UP at biopsy.

5. Renal Survival In Patients With IgAN According To The Oxford Classification

As shown in Figure 2, Kaplan-Meier revealed that S (log-rank, $\chi^2=14.796, P<0.001$, Figure 2C), T
($\chi^2=48.976, P<0.001$, Figure 2D), were associated with renal survival. M ($\chi^2=1.459,
P=0.477$, Figure 2A), E ($\chi^2=2.399, P=0.121$, Figure 2B) and C ($\chi^2=6.218, P=0.054$, Figure 2E) were
not associated with renal outcome.

6. Cox Regression Analysis Of Oxford Classification Associated With Renal Outcomes

The Cox regression analysis results are shown in Table 5. Univariate Cox regression analysis also
revealed that M [hazard ratio (HR) 2.2, 95% confidence interval (CI): 1.5–3.3, $P<0.001$], S (HR 3.1, 95% CI, 2.0
–4.7, $P<0.001$), T (HR 7.9, 95% CI, 4.7–13.4, $P<0.001$) and C (HR 3.4, 95% CI, 1.8–6.2, $P<0.001$) were
associated with renal outcome. In multivariate Cox analysis, after adjustment by Cox regression
model, S (HR 2.7, 95% CI, 1.8–4.2, $P<0.001$) and T (HR 6.6, 95% CI, 3.9–11.3, $P<0.001$) remained as
independent predictors of renal outcome at the time of biopsy.

7. Predictive value of M-E and C lesions between immunosuppressive and without
immunosuppressive groups

We further assessed the predictive value of lesions (M-E and C) in patients without
immunosuppression to assess their natural predictive value. Individuals with C lesions without
immunosuppression experienced a worse survival from a combined event (Figure 3E), but this difference disappeared after the use of any immunosuppressants (Figure 3F). The predictive value of M and E lesions was not changed by adding immunosuppressants (Figure 3A-D).

Discussion

This study investigated the clinical and histopathologic predictors of a poor prognosis in pediatric patients with IgAN. The median duration from onset to renal biopsy was 12 months in our cohort. An early diagnosis seems to be the major reason for a low frequency of chronic and severe lesions such as S,T and C lesions. In our cohort, we confirmed S and T lesions were shown to be independent risk factors associated with renal outcomes. C lesion enhanced the ability to predict progression only in those who did not receive immunosuppression. M and E lesions were not significant variable, which may lose their predictive values because of the low percentage in the cohort. The independent predictive value of pathology MEST-C score is reduced by immunosuppressive therapy.

We confirm that MAP was significantly correlated with M, E, T and C lesions. eGFR was significantly correlated with S, T and C lesions. UP and all pathological indexes were significantly correlated. Our study indicates that UP increases, BP increases and eGFR decreases when pathological types of S, T and C lesions occur, which is consistent with other findings. When the patient reached ESRD, the blood pressure control rate decreased. The uncontrollable hypertension, in turn, acts on the kidney, further aggravating glomerular hyperfiltration, glomerulosclerosis and renal artery damage[7]. For the control target of blood pressure in IgAN, the KDIGO guidelines[8] pointed out that when 24h-UP > 0.3g/d, the recommended target BP was < 130/80 mmHg, and when 24h-UP > 1g/d, the recommended target BP was < 125/75mmHg. It also shows that it is important to control BP in the early stage of IgAN. Bellur et al[9] findings showed that S were strongly associated with proteinuria and lower eGFR levels, which was consistent with our conclusion. Previous studies[10] have shown that, T lesion was an independent risk factor for poor renal prognosis and associated with BP. Some scholars[11, 12] had found that the level of eGFR was lower in patients with IgAN with extensive crescent formation, and there was a negative correlation between eGFR and the proportion of crescents. From the above, it can be concluded that the most significant risk factors for the progression of IgAN (UP, eGFR, MAP)
are significantly correlated with the pathological damage found by renal biopsy, which reflects the value of the combination of clinical and pathological risk factors in judging the prognosis of IgAN patients.

M lesion were found in 29% of patients but could not independently predict renal outcomes, whether or not immunosuppressive therapy. M lesion may lose predictive value because of the low percentage in our study. The value of M lesion as an independent risk for progression is debated. The VALIGA cohort[13] and a Chinese adult cohort[14] confirmed E lesions as a significant factor for progression. M was also reported to have lost predictive value in patients receiving immunosuppressive therapy[15].

E lesion were found in 35% of patients but could not independently predict renal outcomes in our cohort, whether or not immunosuppressive therapy. The E lesion was not predictive of outcomes in the original Oxford Classification cohort[16] and this was also true in most studies. However, 2 studies[17, 18] which no patients received immunosuppression therapy both reported that E1 was independently associated with more rapid loss of renal function and worse renal survival. These studies indirectly suggested that proliferative lesions are treatment-responsive. But this was not the case in our cohort.

Our data showed a correlation between S and renal prognosis, which is further confirmed that S is a definite index to judge the prognosis. Many data from the children's cohort have confirmed the independent predictive value of S lesion. Children's cohort from France confirmed that S lesions were the only histological variable predicting a decline in renal function and were not associated with clinical data at the time of renal biopsy and whether they received immunosuppressive therapy[19]. Studies[20] have shown S lesion could result from an acute condition, driven by endocapillary hypercellularity, or as a continuous cross talk between mesangial cells and podocytes. So it has also been suggested that the association of S1 lesion with M1 and/or E1 lesions needs special attention in children with active glomerular lesions.

T lesions were confirmed as risk factors for poor prognosis, which is consistent with almost all previous adult validation studies. However, most children validation studies, such as Japan
cohort[21], Sweden cohort [22] and VALIGA cohort[13], did not confirm that T lesion could maintain independent predictive value in children. Only the cohort from China by Le et al[23] and our cohort confirmed that T lesion have independent predictive value in children population. This was likely due to the limited number of patients reaching end points and shorter follow-up time.

49% of the patients had C lesion, with 28% having crescents in 10% of glomeruli, proving that most patients had fewer crescents. The presence of crescents portended a higher likelihood of immunosuppression. This study concluded that the presence of any crescents was associated with a worse renal outcome only in those patients not receiving immunosuppression. Immunosuppressive therapy can reverse the prognosis of C and improve the prognosis of kidney, indirectly suggesting the role of C in judging the prognosis of kidney, so C may also become one of the indications of immunosuppressive therapy.

The validation differences among the above different child cohorts are mainly related to the regional and ethnic differences in IgAN, the selection criteria, follow-up time and treatment measures of each study, which emphasizes the need to generate a large database for IgAN children to address the problem of insufficient statistical power due to the small number of progressive cases, especially the relatively short follow-up period.

Our cohort validated the significance of Oxford classification in a large number of Chinese IgAN children. A comprehensive analysis of the renal pathological features and clinical conditions represented in the cohort suggests that Oxford classification must be considered in conjunction with clinical features (including proteinuria levels and eGFR values) and treatment given after renal biopsy. This also suggests that treatment operations after biopsy may regulate some pathological risk factors. Through the study of the clinical and pathological characteristics of IgAN, to explore its risk factors and its impact on disease progression, the level of diagnosis and treatment of IgAN will ultimately be improved.

The limitations of this study must be recognized. First, the retrospective design made difficult the control over the variables measured. Second, our results may not be extrapolated to other ethnic populations because a prior study suggested a geographical variability in long-term outcomes of
IgAN.Final, because of the limitations of retrospective studies, not all patients treated with RASB may weaken the rigor of the study. However, some features of this study may increase the strength of these findings, including the large set of data collected over many years and long-term follow-up by the same team with a well-established clinical protocol, as well as the careful re-evaluation of all renal biopsies by two expert pathologist blinded to clinical data and outcome.

Conclusions
In conclusions, our cohort confirmed S and T lesions were shown to be independent risk factors associated with renal outcomes. C lesion enhanced the ability to predict progression only in those who did not receive immunosuppression. M and E lesions were not significant variable, which may lose their predictive values because of the low percentage in the cohort. The independent predictive value of pathology MEST-C score is reduced by immunosuppressive therapy.

Declarations
1. Ethics approval and consent to participate

The protocol followed in the present study was approved by the Jinling Hospital Ethics Committee on Human Experimentation (NO.2019NZGKJ-169). Due to the retrospective nature of the study, written informed consent for participation in the study was waived.

2. Authors’ contributions

HW, ZX and CG performed the data collection and analysis and participated in manuscript writing. PZ, XY, RW, MW and YP performed the database setup and statistical analysis. HW, ZX and CG participated in the study design and coordination and helped to draft the manuscript. All of the authors have read and approved the final manuscript.

3. Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

4. Consent for publication

Not applicable

5. Competing interests
The authors declare that they have no competing interests.

6. **Acknowledgements**

Not applicable.

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Tables

Table 1. Baseline and follow-up characteristics (n=1243)

| At renal biopsy                                                                 | Values at renal biopsy |
|--------------------------------------------------------------------------------|------------------------|
| Female, %                                                                       | 32                     |
| Age, yr                                                                         | 14±4                   |
| Duration from onset to renal biopsy (months)                                    | 12.0(0.8,96.5)         |
| eGFR, ml/min per 1.73 m²                                                        | 102 ± 20               |
| MAP, mmHg                                                                       | 89±16                  |
| Proteinuria, g/day per 1.73 m²                                                  | 0.6 (0.3–1.4)          |
| Follow-up parameters                                                            | Values during follow-up|
| Length of follow-up, months                                                    | 86.8(54.7–140.2)       |
| RASB, %                                                                         | 70                     |
| Any immunosuppression, %                                                        | 64                     |
| GC                                                                              | 45                     |
| GC+IS                                                                           | 19                     |
| Combined event, %                                                               | 14                     |
| ESRD, %                                                                         | 6.6                    |
| 50% reduction in initial eGFR,%                                                 | 7.2                    |

Values are expressed as mean±SD, medians (interquartile ranges), or percentages.

eGFR, estimate glomerular filtration rate. MAP, mean arterial pressure. RASB, Renin angiotensin aldosterone system blockade. GC, glucocorticoid. IS, immunosuppressant.

Table 2. Pathological findings at the time of biopsy in children with IgA nephropathy (n=1243)

| Pathology findings                                                                 | Values at renal biopsy |
|-----------------------------------------------------------------------------------|------------------------|
| the number of glomeruli per biopsy.                                                | 20.4±4.7               |
| MEST-C score                                                                      | % of total biopsies    |
| M1                                                                                | 29                     |
| E1                                                                                | 35                     |
| S1                                                                                | 37                     |
| T1                                                                                | 23                     |
| T2                                                                                | 4.3                    |
| C1                                                                                | 44                     |
| C2                                                                                | 4.6                    |
| Deposition site of immunoglobulins                                                | % of total biopsies    |
| Pure-mesangium                                                                   | 68                     |
| Mesangium+ capillary loop                                                         | 32                     |
| Immunoglobulins deposits                                                          | % of total biopsies    |
| Glomerular IgG deposition                                                         | 25                     |
| Glomerular IgM deposition                                                         | 44                     |
| Glomerular C3 deposition                                                         | 84                     |
| Glomerular C4 deposition                                                           | 1.1                    |
| Intensity of IgA                                                                  | % of total biopsies    |
| ++                                                                               | 5.6                    |
| +++                                                                              | 13                     |
| ++++                                                                             | 81                     |

Values are expressed as means±SD or percentages. Pathology findings are defined according to
Oxford classification [4].

Table 3 Comparison of all kinds of lesions with different time of onset to renal biopsy (n=1243)

| Variables | Time from onset to renal biopsy | \(c^2\) | \(P\) |
|-----------|--------------------------------|--------|-----|
| \(M0/M1\) | \(\leq 12\) months | 449/172 | 433/189 | 1.1 | 0.296 |
|          | 12 months | 411/210 | 401/221 | 0.4 | 0.525 |
| \(E0/E1\) | \(\leq 12\) months | 554/67 | 235/387 | 354.5 | 0.001 |
|          | 12 months | 595/21/5 | 315/259/48 | 323.3 | 0.001 |
| \(S0/S1\) | \(\leq 12\) months | 205/106 | 235/387 | 354.5 | 0.001 |
|          | 12 months | 506/104/11 | 138/438/46 | 437.6 | 0.001 |

Pathology findings are defined according to Oxford classification [4].

Table 4 Single Factor Analysis of Oxford Classification and Clinical Indicators

| Clinical indicators | MAP (mmHg) | eGFR (ml/min/1.73m²) | 24h-UP (g/24h/1.73m²) |
|---------------------|------------|-----------------------|------------------------|
|                     | \(r\)  | \(P\)  | \(r\) | \(P\)  | \(r\) | \(P\)  |
| \(M1\)              | 0.342 | 0.001 | 0.044 | 0.133 | 0.569 | 0.001 |
| \(E1\)              | 0.338 | 0.001 | -0.331 | 0.389 | 0.527 | 0.001 |
| \(S1\)              | 0.541 | 0.042 | -0.744 | 0.007 | 0.604 | 0.001 |
| \(T1-2\)            | 0.532 | 0.001 | -0.578 | 0.001 | 0.689 | 0.001 |
| \(C1-2\)            | 0.549 | 0.008 | -0.447 | 0.001 | 0.447 | 0.001 |

Pathology findings are defined according to Oxford classification [4].

Table 5. Factors at biopsy influencing renal outcome from ESRD or 50% drop in eGFR by univariate and multivariate Cox regression

| Risk factors | Univariate factor analysis | Multifactorial factor analysis |
|--------------|---------------------------|-------------------------------|
|              | HR | 95%CI | \(P\) | HR | 95%CI | \(P\) |
| \(M\)        | 2.2 | 1.533 | 0.000 | 2.0 | 1.230 | 0.059 |
| \(E\)        | 1.4 | 0.921 | 0.139 |     |     |     |
| \(S\)        | 3.1 | 2.047 | 0.000 | 2.7 | 1.842 | 0.000 |
| \(T\)        | 7.9 | 4.713 | 0.000 | 6.6 | 3.911 | 0.000 |
| \(C\)        | 3.4 | 1.862 | 0.000 | 1.8 | 1.225 | 0.212 |
The distribution of the percentage of crescents observed in every children
Kaplan-Meier revealed that S ($\chi^2=14.796, P<0.001$, Figure 2C), T ($\chi^2=48.976, P<0.001$, Figure 2D), were associated with renal survival. M[$\chi^2=1.459, P=0.477$, Figure 2A], E ($\chi^2=2.399, P=0.121$, Figure 2B) and C($\chi^2=6.218, P=0.054$, Figure 2E) were not associated with renal outcome.
Individuals with C lesions without immunosuppression experienced a worse survival from a combined event (Figure 3E), but this difference disappeared after the use of any immunosuppressants (Figure 3F). The predictive value of M and E lesions was not changed by adding immunosuppressants (Figure 3A-D).