Clinical implication of crescentic lesions in immunoglobulin A nephropathy

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ABSTRACT

Background. To date, there has been much controversy about the role of crescentic lesion as a significant prognostic factor in immunoglobulin A nephropathy (IgAN). This study evaluated whether crescentic lesions predict adverse renal outcomes in IgAN patients.

Methods. A total of 430 patients with biopsy-proven IgAN between January 2000 and December 2009 were included. Histological variables of the Oxford classification (Oxford-MEST) and the presence of crescents were assessed. The primary endpoint was a 50% decline in estimated glomerular filtration rate.

Results. Of the 430 patients, 81 (18.8%) had a crescentic lesion. During a mean follow-up of 61 months, the primary outcome occurred in 19 (23.5%) patients with crescents compared with 40 (11.5%) patients without crescents (P = 0.01). A Kaplan–Meier plot showed that the 10-year renal survival rate was significantly lower in patients with crescents than patients without crescents (P = 0.01). However, in a multivariable Cox analysis which included clinical factors and the Oxford-MEST, crescents were not significantly associated with an increased risk of developing the primary outcome [hazard ratio: 0.71, 95% confidence interval (CI) 0.36–1.41, P = 0.33]. Furthermore, adding crescents to the Oxford-MEST did not improve the discriminative ability for the prediction of renal outcomes [c-statistic: 0.86 (0.81–0.91) vs. 0.86 (0.80–0.91), P = 0.21].

Conclusion. Crescentic lesion was not an independent prognostic factor, suggesting that crescents have limited value in predicting renal outcomes of IgAN.

Keywords: crescents, immunoglobulin A nephropathy, outcome, Oxford classification

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide [1]. Patients with IgAN have a complex clinical course, which varies from persistent asymptomatic microscopic hematuria to progressive renal failure [2–4]. Previous studies have indicated a variable prognosis that 6–43% of IgAN patients will eventually develop end-stage renal disease (ESRD) over a period of 10 years [5–8]. Hypertension, heavy proteinuria and impaired renal function at the time of diagnosis and during the follow-up were well-established clinical risk factors for the progression of IgAN [4–6, 8, 9]. Recently, the Working Group of the International IgAN Network and the Renal Pathology Society proposed the Oxford classification, which provides an integrated perspective on the prognostic value of histological lesions [10, 11]. They identified four histological lesions associated with poor renal outcomes: mesangial hypercellularity, endocapillary proliferation, segmental sclerosis and tubular atrophy/interstitial fibrosis [10, 11].

Interestingly, a rapidly progressive course with crescentic formation is a rare clinical manifestation of IgAN, accounting for <5% of the whole population [12, 13]. Crescents have been reported to be associated with a poor prognosis, and patients with such lesions often require intensive immunosuppressive treatments [14–22]. Of note, the Working Group of the Oxford classification excluded patients with rapidly progressive disease and an initial estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m². Crescents were also excluded from this classification system due to their low prevalence in the enrolled cohort [10]. However, >90% of cases of IgAN generally do not have a rapidly progressive nature, and crescents are often seen in patients who have less advanced...
histology and relatively preserved kidney function. To date, the clinical implication of crescentic lesions in these patients has not been clearly defined. Since the Oxford classification was introduced, subsequent validation studies have evaluated the significance of crescents in IgAN using this classification system [22–27]. Katafuchi et al. [22] demonstrated that crescent was an independent predictor of renal outcomes in Japanese IgAN. However, several other studies failed to reveal the prognostic value of crescents [24, 25, 27]. The conflicting results of previous observations prompted us to explore whether crescents can predict adverse renal outcomes in our cohort of patients with IgAN. To this end, in this study, we incorporated crescentic lesions into the Oxford-MEST classification and investigated their prognostic value.

MATERIALS AND METHODS

Subjects

Four hundred and ninety-five patients were diagnosed with IgAN by renal biopsy at Yonsei University Health System (YUHS) between January 2000 and December 2009. Patients with Henoch-Schonlein purpura were considered ineligible. Among these patients, we excluded patients who were <20 years of age or >75 years, those who had an inadequate biopsy sample with ≤7 glomeruli, and those with the secondary causes of mesangial IgA deposition, such as IgA-dominant acute post-infectious glomerulonephritis, systemic lupus erythematosus or chronic liver disease. Patients who were followed up for <6 months were excluded, whereas those who developed ESRD within 6 months after the diagnosis of IgAN were included. Therefore, the remaining 430 patients were analyzed in this study (Figure 1). We carried out the study in accordance with the Declaration of Helsinki, and the study was approved by the Institutional Review Board (IRB) of the YUHS Clinical Trial Center. Since the current study was a retrospective study and the study subjects were de-identified, the IRB waived the need for written consent from the patients.

Clinical and biochemical data collection

Demographic and clinical data, such as age, sex, date of renal biopsy, and episodes of gross hematuria, were collected at the time of biopsy. Hypertension was defined as a systolic blood pressure (BP) >140 mmHg or a diastolic BP >90 mmHg, or the need for antihypertensive medication to maintain BP below these levels. The following laboratory data were measured from blood and urine samples: hemoglobin, blood urea nitrogen, creatinine, albumin, total cholesterol and urinary protein-to-creatinine ratio (UPCR). The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [28]. Our institution started to use IDMS-traceable serum creatinine in March 2011. Therefore, to use the CKD-EPI equation, we multiplied the serum creatinine values by 0.95. In addition, data of mean arterial pressure (MAP), UPCR, eGFR and treatment modalities were collected every 6 months until the last follow-up. The mean values of MAP and UPCR during the follow-up were indicated as time averaged-MAP (TA-MAP) and time averaged-proteinuria (TA-P). The decline rate of eGFR was expressed as the slope of eGFR, estimated by linear regression and the principle of least squares for each patient. Patients who received glucocorticoids, other immunosuppressive treatments or antihypertensive drugs were defined as those treated for >6 months.

Histopathological variables

All renal biopsy specimens were re-assessed by one pathologist blinded to the patients’ clinical data using the Oxford classification [10, 11]. Mesangial cellularity was scored for each glomerulus by assessing the most cellular mesangial area, that is, not adjacent to the vascular stalk (<4 mesangial cells per mesangial area = 0; 4–5 mesangial cells = 1; 6–7 mesangial cells = 2; ≥8 mesangial cells = 3). The mesangial hypercellularity score is the mean score for all glomeruli. A score of 0.5 or less was defined as M0, and a score >0.5 was defined as M1. Segmental glomerulosclerosis and endocapillary hypercellularity were classified as either present (S1 and E1) or absent (S0 and E0). Tubular atrophy/interstitial fibrosis was categorized according to the percentage of the renal cortical area involved into the following: T0 (0–25% of cortical area), T1 (26–50%) or T2 (>50%). Extracapillary proliferation involving cellular and fibrocellular crescents and its presence was defined as C1.

Study outcomes

The primary outcome was a 50% decline in eGFR and the secondary outcome was the onset of ESRD. ESRD was defined as the initiation of renal replacement therapy, including dialysis or renal transplantation. We also evaluated the decline rate of eGFR according to the Oxford-MEST classification and crescents.

Statistical analysis

Statistical analysis was performed using the Stata software (version 11.0, StataCorp). Continuous and categorical variables were expressed as means ± standard deviation or a number (percentage). The Kolmogorov–Smirnov test was...
used to analyze the normality of the distribution of parameters. Data that did not show a normal distribution were expressed as median and inter-quartile range. Subjects were divided into two groups according to the presence of crescents. The two groups were compared using the t-test or Chi-squared test. Differences among the three groups of tubular atrophy/interstitial fibrosis were compared by ANOVA with Bonferroni post hoc tests. To determine an independent association between histopathological features and the decline rate of renal function, univariate and multivariate linear regression analyses were used. Renal survival curves were generated by the Kaplan–Meier method, and between-group survival was compared by a log-rank test. Independent prognostic values of clinical and pathological variables were ascertained by Cox proportional hazards regression models. Cox models were constructed to include clinical data, histological variables of the Oxford classification, and crescents, consecutively. Harrell’s C index of each model was calculated to investigate the discriminatory ability. Using this index, we determined whether histological variables have additive value to clinical variables in the prediction of renal survival. A P-value <0.05 was considered statistically significant.

### RESULTS

#### Baseline characteristics according to the presence of crescentic lesions

The baseline characteristics of subjects are shown in Table 1. The mean age was 34.9 ± 11.7 years (19–73 years), and 227 (52.8%) were male. At the time of biopsy, the mean MAP and eGFR was 94.6 ± 11.3 mmHg and 80.5 ± 24.1 mL/min/1.73 m². The median UPCR was 0.8 (0.3–1.8) g/g. Of the 430 patients, 81 (18.8%) patients had a crescentic lesion. The frequency distribution according to the percentage of glomeruli showing crescents is shown in Figure 2. Among 81 patients with C1, 35 (43.2%) patients had <10% crescents of glomeruli and 3 (3.6%) patients had ≥50% crescents of glomeruli. These patients had higher levels of UPCR, blood urea nitrogen, total cholesterol, and creatinine, but they had lower albumin levels and eGFR than patients without crescents. During the follow-up, renin–angiotensin system blockades and glucocorticoid treatment were prescribed more often to patients with crescents. Furthermore, the proportions of M1, E1, S1, T1 and T2 were significantly higher in patients with crescents.

#### Comparison of clinical parameters according to pathological features at baseline and during the follow-up

The baseline distribution of pathological variables and the comparison of clinical data according to the Oxford-MEST and crescents are depicted in Table 2. At the time of biopsy, patients with a high score for each MEST lesion on the Oxford classification and crescents had greater UPCR values than patients without such components. Furthermore, baseline eGFR was significantly lower in patients with E1, S1, T1/T2 and C1. Similar to baseline UPCR, TA-P was significantly higher in patients with a high score for individual MEST lesions on the Oxford classification and crescents. The decline in eGFR was greater in patients with M1, S1 and T1/T2 than in patients with M0, S0 and T0, respectively. However, the rate of decline in eGFR did not differ between patients with C0 and those with C1. Finally, a multivariate linear regression analysis was performed to identify pathological variables strongly associated with a decline in kidney function. After adjustment for each MEST lesion and baseline clinical variables including MAP, UPCR and eGFR, segmental sclerosis (S1 vs. S0, β = −0.114, P = 0.03) and tubular atrophy/interstitial fibrosis (T1 + T2 vs. T0, β = −0.106, P = 0.04) had significant relationships with the slope of eGFR decline. Of note, crescents were not associated with the rate of eGFR decline in either univariate or multivariate analysis (β = −0.047, P = 0.33; β = 0.016, P = 0.75, respectively).

#### Prognostic value of crescents for renal outcomes

During a mean follow-up of 61.0 ± 32.3 months, 19 (23.5%) patients with crescents reached the primary endpoint, compared with 40 (11.5%) patients without crescents (P = 0.01). There was no patient who progressed to ESRD before reaching a 50% decline in eGFR. ESRD occurred in 17 (21.0%) with crescents, when compared with 32 (9.2%) without crescents (P = 0.01) (Table 3). A Kaplan–Meier plot also showed that the 10-year renal survival rate was significantly lower in patients with crescents than patients without crescents (Figure 3, P = 0.01).

To determine the prognostic value of crescents for renal outcomes, Cox proportional hazard models were developed (Table 4). Using unadjusted Cox models, we found that MAP, eGFR, UPCR and all pathological variables were significantly associated with adverse renal outcomes (data not shown). In a multivariable Cox model adjusted for only clinical factors, the risk of reaching the primary endpoint did not differ between patients with C1 and patients with C0 [hazard ratio (HR) 0.98, 95% confidence interval (CI) 0.55–1.74, P = 0.9] (model 2). Furthermore, when added to model 3, C1 was not associated with an increased risk of developing the primary outcome (C1, HR: 0.71, 95% CI: 0.36–1.41, P = 0.33), whereas tubular atrophy/interstitial fibrosis remained a significant predictor (T1, HR: 3.98, 95% CI: 1.58–10.07, P = 0.003; T2, HR: 5.41, 95% CI: 2.07–14.17, P = 0.001) (model 4). Although crescentic lesions were further classified into an absence of crescents, 0–10%, and ≥10% of glomeruli affected, crescents ≥10% were not associated with adverse renal outcomes after adjusting for clinical factors and the Oxford-MEST score (HR: 0.78, 95% CI: 0.36–1.63, P = 0.51, data not shown).

#### Additive prognostic value of pathological variables for the prediction of renal outcomes

To assess the predictive power of histological parameters, we calculated Harrell’s C index for each multivariate Cox regression model (Table 5). Compared with the c-statistic of model 1 which included baseline clinical variables only (c-statistic, 0.84; 95% CI: 0.77–0.90), the c-statistic of model 3 in which the Oxford-MEST lesions were added was significantly increased (c-statistic, 0.86; 95% CI: 0.81–0.91; P = 0.03). However, adding crescents to model 1 (model 2; c-statistic, 0.82; 95% CI: 0.77–0.87; P = 0.32) or model 3 (model 4; c-
DISCUSSION

Given previous conflicting results, the prognostic significance of glomerular crescents in IgAN has not yet been established [10, 11, 14–27]. In this study, we showed that a 50% decline in eGFR and ESRD occurred more frequently in patients with crescents than in those without crescents. However, in the multivariate Cox analysis adjusted for clinical factors and/or the Oxford-MEST score, crescents were not independently associated with renal survival. Moreover, c-statistic analysis clearly demonstrated that adding crescents did not improve the predictive power of the model with clinical factors and the Oxford-MEST score. These findings suggest that crescents have limited value in predicting renal outcomes of IgAN.

Over the past few decades, there has been a growing interest in the clinical significance of crescents in patients with IgAN. Early case series indicated that the presence of crescents was a poor prognostic factor and was associated with proteinuria and hypertension [14–21]. Some of these studies raised concern about small and focal crescents, showing that crescents in only 10% of glomeruli might portend an unfavorable
prognosis [18, 20]. However, many studies did not consider other well-known pathological factors associated with poor outcomes such as tubulointerstitial fibrosis in the analyses [17, 19, 21]. In fact, the prognostic significance of crescents was mostly seen in an unadjusted model [14–21]. Since the Oxford classification was proposed, many validation studies have been carried out and some of them have attempted to clarify the clinical implications of crescents in IgAN. A recent study by Katafuchi et al. [22] involving 702 Japanese IgAN patients showed that crescents were significantly associated with the development of ESRD after adjustment of the Oxford-MEST score. Interestingly, such an association was only evident in patients who did not meet the inclusion criteria of the Oxford classification, whereas it was not seen in patients who met them, suggesting that a discrepancy between the original study of the Oxford classification and their observation is likely due to different inclusion criteria. Indeed, patients with proteinuria <0.5 g/day and those with an eGFR <30 mL/min/1.73 m² were not included in the Oxford classification [10, 11]. However, this finding was not corroborated by other validation studies of the same classification [24, 25, 27]. In particular, two large Chinese cohort studies found that, using the same inclusion criteria of the Oxford classification, crescents were not significant in predicting renal outcomes [24, 27]. Consistent with their findings, we failed to find a prognostic value of crescents. Of note, the characteristics of our study subjects were similar to those of the Oxford cohort, because this study included five (1.2%) patients with an eGFR <30 mL/min/1.73 m². Therefore, it is possible that crescents may have a prognostic value in severe IgAN as suggested by Katafuchi et al.

In general, crescentic glomerulonephritis refers to >50% of glomeruli with crescents [29]. Recent validation studies of the Oxford classification included any extracapillary proliferation [22, 24, 25, 27]. In these studies, there were few patients who had crescents involving >50% of glomeruli and showed a rapidly progressive nature. Thus, the majority of patients did not have ‘classic’ crescentic glomerulonephritis. This may explain the lack of association between crescents and renal outcomes in the most recent studies including ours. To date, it is uncertain whether a small number of crescents may contribute to the deterioration of kidney function, particularly in typical IgAN patients with a slowly progressive course over a long period of time. Katafuchi et al. [22] suggested that the percentage of crescents could be more associated with poor renal outcomes than its mere presence, and the cutoff point as a prognosticator might be ~10%. Based on their results, we
further analyzed our data according to the percentage of crescents, which was the absence of crescent, 0–10%, and ≥10% of glomeruli affected. However, we failed to find a prognostic significance for crescents. Even crescents ≥10% were not associated with renal outcomes. Relevant to our finding is a recent study by Shi et al. [24] showing that crescents with a high

**FIGURE 3:** Kaplan–Meier plots of renal survival for primary outcome according to histological variables of the Oxford classification, and crescents. (A) mesangial hypercellularity, (B) endocapillary proliferation, (C) segmental glomerulosclerosis, (D) tubular atrophy/interstitial fibrosis and (E) crescents. Patients with mesangial hypercellularity, segmental glomerulosclerosis, endocapillary proliferation, tubular atrophy/interstitial fibrosis and crescents had significantly lower renal survival than those without such lesions (all P < 0.05).
extracapillary glomerular activity index did not predict adverse outcomes. All of these findings taken together suggest that a small numbers of crescents in slowly progressive IgAN appears to be less important than many, as previously suggested [24, 27].

Another main finding of this study was that four pathological features of the Oxford classification had additional predictive value to clinical risk factors, but adding crescents showed no benefit in predicting prognosis in IgAN. Although previous studies have emphasized the predictive value of clinical variables at onset and during the follow-up [7, 30], whether pathological features have an independent prognostic value remains controversial [31, 32]. In a study by Alamartine et al. [23], multivariate analysis found that eGFR at baseline was the only prognostic factor and pathological lesions had no independent influence. They suggested that renal function at baseline might be of greater importance than pathological lesions. In contrast, Yau et al. [25] showed that the discriminative strength was comparable between clinical and pathological variables. In the present study, Harrell’s C index was significantly increased when four pathological features of the Oxford classification were added to the model with clinical factors only, suggesting that pathological variables had an additional prognostic value to clinical risk factors for the prediction of renal outcomes. Nevertheless, adding crescents did not provide additional benefit in the discrimination of renal outcomes compared with the Oxford-MEST score.

Previous validation studies of the Oxford classification showed that, besides T lesion, M or E lesion was an independent predictor of renal outcome [10, 22, 24, 25, 27]. In the present study, S and T lesions had significant relationships with the slope of eGFR decline in accordance with the original Oxford study [10]. In addition, T lesion was the only pathological prognostic factor of the primary outcome in multivariable Cox analyses. This discrepancy is partly attributed to the relatively low proportion of E1 lesion and a significant difference in corticosteroid use according to some pathological features in our study. In fact, steroid treatment bias was observed for E and C lesions, whereas there was no such association for M and S lesions (data not shown). Unfortunately, detailed analysis on the relationship between pathological features and responsiveness to immunosuppression is limited by the retrospective nature of our study and a small number of patients with E1 or C1 lesion, which might result in a lack of statistical power. In addition, treatment decisions are largely based on clinical features, not pathological features and there is no pre-set indication for the use of corticosteroids in IgAN according to pathological features. Given the strengths of the Oxford classification that specifically recognize pathological features associated with progression, further well-designed randomized controlled studies are required to delineate the relationships between the Oxford-MEST lesions and treatment responsiveness.

This study has several limitations. First, since one pathologist reviewed and scored all pathological variables, interobserver reproducibility was not evaluated. Second, although this study enrolled patients who progressed to ESRD, our cohort had a small number of patients with advanced disease. It should be noted that the prognostic significance of crescents was only evident in patients with a GFR <30 mL/min/1.73 m².

Table 4. Multivariate analyses of pathological findings and baseline clinical variables for the primary outcome

<table>
<thead>
<tr>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 4&lt;sup&gt;d&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
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<tr>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td>MAP (per 1 mmHg)</td>
<td>0.99 (0.96–1.02)</td>
<td>0.38</td>
<td>0.99 (0.96–1.02)</td>
</tr>
<tr>
<td>UPCR (per 1 g/g)</td>
<td>1.34 (1.21–1.49)</td>
<td>&lt;0.001</td>
<td>1.34 (1.21–1.49)</td>
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<tr>
<td>eGFR (per 1 mL/min/1.73 m²)</td>
<td>0.94 (0.93–0.96)</td>
<td>&lt;0.001</td>
<td>0.94 (0.93–0.96)</td>
</tr>
<tr>
<td>M1 (versus M0)</td>
<td>–</td>
<td>–</td>
<td>0.95 (0.93–0.97)</td>
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<tr>
<td>E1 (versus E0)</td>
<td>–</td>
<td>–</td>
<td>0.95 (0.93–0.97)</td>
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<tr>
<td>S1 (versus S0)</td>
<td>–</td>
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<td>0.95 (0.93–0.97)</td>
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<tr>
<td>T1 (versus T0)</td>
<td>–</td>
<td>–</td>
<td>0.95 (0.93–0.97)</td>
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<tr>
<td>T2 (versus T0)</td>
<td>–</td>
<td>–</td>
<td>0.95 (0.93–0.97)</td>
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<tr>
<td>C1 (versus C0)</td>
<td>–</td>
<td>–</td>
<td>0.95 (0.93–0.97)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Model 1: sex, age and baseline clinical variables (MAP, UPCR and eGFR).
<sup>b</sup>Model 2: Model 1 + C.
<sup>c</sup>Model 3: Model 1 + M, E, S, T.
<sup>d</sup>Model 4: Model 1 + M, E, S, T, C.

Table 5. C-statistics for prediction of the primary outcome using multivariate Cox’s regression models

<table>
<thead>
<tr>
<th>Model</th>
<th>C-statistics (95% CI)</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
<td></td>
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<td>P for difference in C-statistics compared with models</td>
<td></td>
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<tr>
<td>Model</td>
<td>C-statistics (95% CI)</td>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.84 (0.77–0.90)</td>
<td>NA</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.82 (0.77–0.87)</td>
<td>0.32</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.86 (0.81–0.91)</td>
<td>0.03</td>
<td>0.03</td>
<td>NA</td>
</tr>
<tr>
<td>Model 4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.86 (0.80–0.91)</td>
<td>0.04</td>
<td>0.04</td>
<td>0.21</td>
</tr>
</tbody>
</table>

<sup>a</sup>Model 1: sex, age and baseline clinical variables (MAP, UPCR and eGFR).
<sup>b</sup>Model 2: Model 1 + C.
<sup>c</sup>Model 3: Model 1 + M, E, S, T.
<sup>d</sup>Model 4: Model 1 + M, E, S, T, C.

CI, confidence interval; NA, not applicable.
in the study of Katafuchi et al. [22]. In addition, early published data in favor of crescents as a poor prognosticator revealed that the study subjects had features of ‘classic’ crescentic glomerulonephritis with a rapid deterioration of kidney function. In our study, there were only three patients who showed a rapidly progressive course. In this regard, our cohort may not be appropriate for investigating the significance of crescents in IgAN. Third, there was a relatively small number of crescents in our study. Among 430 patients, 18.8% had crescents, which is similar to the prevalence in the USA, Brazil and several Asian countries [17, 19, 21, 25]. Interestingly, the prevalence of crescents was reported to be highly variable. A French study reported that only 5% of patients had crescents [23], whereas recent Chinese and Japanese studies showed that ~60% had crescents [22, 24, 27]. In fact, IgAN is considered to have geographic variability and ethnic differences in progression [4, 33]. In addition, different biopsy practice policies may lead to diverse clinical and pathological features at the onset of IgAN, which can thus introduce potential lead-time bias in the estimates of kidney survival [3]. Finally, the role of immunosuppressive therapy is not clear in this study. Previous studies showed that immunosuppressive drugs such as corticosteroids with or without cyclophosphamide decreased interstitial cell infiltration and crescents and improved renal outcomes [17, 18, 34, 35]. These findings provided the rationale for the recommendation by the kidney disease: improving global outcomes (KDIGO) guideline, which is the use of steroids and cyclophosphamide in patients with rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis [36]. Nevertheless, most of the previous studies were not randomized controlled trials, and they were also limited by a small sample size and a lack of long-term follow-up data, thus the evidence level was low (2D). In our study, patients with crescents also received more immunosuppressive treatment. However, immunosuppressive treatment was not associated with an improved renal outcome in a subgroup analysis involving only patients who had crescents (HR: 2.81; 95% CI: 0.28–28.26; P = 0.38; data not shown). Owing to the retrospective design of our study, the impact of immunosuppression on pathological features and renal outcomes could not be clarified.

In conclusion, the present study showed that crescentic lesion was associated with developing adverse outcomes in univariable analysis, but such an association disappeared after adjusting for clinical factors and Oxford-MEST lesions. Furthermore, crescents did not improve the predictive power of the model in c-statistic analysis. However, it remains to be further elucidated whether crescents have clinical implications in severe IgAN or IgAN with a rapidly progressive nature. Our finding limits the utility of crescents as a prognosticator for future renal outcomes in IgAN.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

Prevalence and severity of oral disease in adults with chronic kidney disease: a systematic review of observational studies

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ABSTRACT

Background. Oral disease may be increased in people with chronic kidney disease (CKD) and, due to associations with inflammation and malnutrition, represents a potential modifiable risk factor for cardiovascular disease and mortality. We summarized the prevalence of oral disease in adults with CKD and explored any association between oral disease and mortality.

Methods. We used systematic review of observational studies evaluating oral health in adults with CKD identified in MEDLINE (through September 2012) without language restriction. We summarized prevalence and associations with all-cause and cardiovascular mortality using random-effects

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