

Risk stratification for progression of IgA nephropathy using a decision tree induction algorithm

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Abstract

Background. Immunoglobulin A nephropathy (IgAN) is the most common form of glomerulonephritis, and many patients are at risk of at least slow progression. However, prediction of the renal outcome in individual patients remains difficult.

Methods. To develop a practical and user-friendly scheme for risk stratification of IgAN patients, data were extracted from a prospective cohort study conducted in 97 clinical units in Japan from 1995. Specifically, we examined deterioration in renal function, defined as doubling of serum creatinine, within 10 years of follow-up in 790 adult IgAN patients without substantial renal dysfunction at baseline using a decision tree induction algorithm.

Results. Recursive partitioning indicated that the best single predictor of renal deterioration was severe proteinuria on urine dipstick testing, followed by hypoalbuminaemia and the presence of mild haematuria for patients with and without severe proteinuria, respectively. Serum total protein levels, diastolic blood pressure and histological grade were placed in the third tier of the decision tree model. With these six variables, patients can be readily stratified into seven risk groups whose incidence of renal deterioration within 10-year follow-up ranges from 1.0% to 51.4%. Logistic regression also identified severe proteinuria, hypoalbuminaemia and mild haematuria as significant predictors of deterioration. Areas under the receiver-operating characteristic curve for the prediction were comparable between the decision tree model and the logistic regression model [0.830 (95% confidence interval, 0.777–0.883) versus 0.808 (95% confidence interval, 0.754–0.861)].

Conclusion. Risk of substantial renal deterioration in IgAN patients can be validly estimated using six predictors obtained from clinical routine.

Keywords: cohort studies; disease progression; IgA nephropathy; prognosis; risk factors

Introduction

Immunoglobulin A nephropathy (IgAN) was described as a new clinical entity in 1968 by Berger and Hinglais [1] and is now the most common cause of idiopathic glomerulonephritis [2–4]. Many studies have evaluated long-term outcomes and prognostic factors of patients with IgAN. Although this disorder is thought to follow a benign course, many patients are at risk for at least slow progression. Furthermore, end-stage renal disease (ESRD) develops in ~15% of cases within 10 years [5]. Several prognostic factors, such as elevated serum creatinine, severe proteinuria, arterial hypertension and histological findings from a renal biopsy, were suggested in the previous studies [5].

Predicting renal outcome in individual patients offers great benefits on determining those who need aggressive therapeutic regimen. We earlier reported a valid scoring system to predict renal outcome in IgAN on the basis of our 7-year follow-up data including all patients followed up with various levels of baseline renal function [6]. Although the estimation was accurate, it was somewhat complex because many predictors were involved with their meticulous classification levels. Additionally, clinicians already know that the patients with azotaemia at their initial visit have a poor renal outcome from their own clinical experiences. The objectives of the current analysis are, therefore, to develop a practical and user-friendly decision tree scheme to stratify the risks of progression of the disease within 10 years of follow-up among biopsy-proven IgAN patients without substantial renal dysfunction.

Methods

Measurement and follow-up of study subjects

Our earlier study [6] proposed a scoring system to predict renal outcome in IgAN based on the follow-up data

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until 2002, 7 years from the beginning of the follow-up. The methods of subject inclusion have been described in the same article. Briefly, 2450 patients with biopsy-proven IgAN from 97 clinical units were followed from 1995 when a nationwide survey on IgAN was jointly conducted by the two research committees on specified intractable diseases organized by the Japanese Government. Follow-up mail surveys to collect information on outcomes such as death, ESRD and serum creatinine were conducted in 1997, 1999, 2002 and 2005 with response rates of 82.5, 95.7, 93.3 and 82.7%, respectively.

The current analysis excluded patients <13 years of age because the glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation formulated using data from adults [7] and not validated among children. We also excluded patients whose estimated baseline GFR was <60 mL/min/1.73 m², and whose serum creatinine was not measured during the latter half of the follow-up period unless they reached the endpoint, substantial renal deterioration.

The baseline data of the patients obtained by reviewing medical records in the nationwide survey in 1995 included sex, age, family history of chronic renal failure and chronic glomerulonephritis, initial clinical manifestations, year of diagnostic renal biopsy, systolic and diastolic blood pressure, urine protein and blood, serum total protein, albumin and creatinine. Proteinuria was semiquantified with a spot urine dipstick test with (–), (±), (+), (++) and (+++) corresponding to <10, 10–29, 30–99, 100–299 and ≥300 mg/dL of urine albumin, respectively. Histological grade at initial renal biopsy was assessed using the criteria from the Joint Committee of the Research Group on Progressive Renal Diseases and the Japanese Society of Nephrology [8]. For GFR estimation, the abbreviated MDRD study equation modified for Japanese patients with chronic kidney disease was applied [9]. The endpoint in the present study was substantial deterioration in renal function, which was defined as doubling of serum creatinine within 10 years. However, even if serum creatinine was more than double the baseline level, the case was not treated as substantial renal deterioration unless above the normal range, ≥1.1 and ≥0.8 mg/dL in men and women, respectively [10].

Development of the decision tree model

The classification tree analysis generates groups of individuals on the basis of a selected criterion, the Gini index, for splitting a group into two to maximize the probability of a single outcome, namely substantial renal deterioration [11,12]. The recursive process of partitioning data continues until the Gini index indicates that the tree fits the information contained in the dataset without overfitting. It can provide a practical model for dichotomous outcomes if the validity of the obtained model is proved sufficient [13]. The missing values were replaced with values minimizing the impurity of the nodes, median values for continuous variables and most frequent categories for categorical variables, or distribution-based estimates.

We constructed 17 candidate models by changing the detailed settings of model construction, such as the manner of

imputation of the missing values and the minimum size of the records in parent and final child nodes. Then, the final model was selected from these candidate models based on the Gini index and the area under the receiver-operating characteristic (ROC) curve for the entire dataset. We also performed a subanalysis for the patients whose data on 24-h urinary protein excretion were available to validate the prediction using dipstick urinalysis.

Evaluation of the decision tree model

The incidence rate of substantial renal deterioration for each risk group, the odds ratios (ORs) with their 95% confidence intervals (CIs) between risk groups and the area under the ROC curve for predicting renal deterioration were calculated. Then, a 5-fold cross-validation was performed to assess the reproducibility of the decision tree model. Overestimation in the original sample was evaluated using the bootstrap in the whole dataset by sampling with replacement for 100 iterations [14,15]. The tree model was fitted to a bootstrap sample to estimate the risk of renal deterioration and evaluated in the bootstrap sample and in the original sample. The performance, the area under the ROC curve in the bootstrap sample represents estimation of the apparent performance, and the performance in the original sample represents test performance. The difference between these performances is an estimate of the optimism in the apparent performance. To estimate the internally validated performance, the average of the optimism is subtracted from the apparent performance. A multivariable logistic regression model was also constructed, and the accuracy of the decision tree model was compared with that of the logistic regression model using the area under the ROC curves.

Statistics and ethics

When demographic and clinical characteristics and baseline laboratory data were compared between patients with and without renal deterioration, Student's *t*-test was used for continuous variables, and Fisher's exact test for categorical variables. Ordinal categories of year of initial renal biopsy, proteinuria and histopathological grade at renal biopsy were replaced by consecutive integers, and the Wilcoxon rank-sum test was applied.

All tests of significance were 2-tailed, and the *P*-values <0.05 were considered statistically significant. Analyses were performed using the STATA 9.2 software (STATA Corporation, College Station, TX, USA) and SAS version 9.1.2 including Enterprise Miner 5.0 (SAS Institute, Cary, NC, USA). This investigation was approved by the Ethics Committee of Kyoto University Graduate School of Medicine and the Ethics Committee of the Juntendo University School of Medicine.

Results

To obtain a dataset for the current analysis, 165 patients with unknown outcomes and two patients with erroneous

Table 1. Baseline characteristics of patients with or without renal deterioration

| Characteristic | Patients with renal deterioration | Patients with stable renal function | P-value |
|--|-----------------------------------|-------------------------------------|---------|
| No. of patients | 68 | 722 | |
| Follow-up period (month) | 90.5 (67–122) | 120 (89–122) | <0.001 |
| Age (year) | 27.7 (21.4–44.1) | 28.2 (20.6–40.7) | 0.55 |
| Women | 34 (50.0) | 426 (59.0) | 0.096 |
| Family history of chronic renal failure | 5 (7.4) | 30 (4.2) | 0.18 |
| Family history of chronic glomerulonephritis | 2 (2.9) | 50 (6.9) | 0.16 |
| Initial manifestation | | | |
| Chance proteinuria | 54 (79.4) | 517 (71.6) | 0.11 |
| Macrohaematuria | 3 (4.4) | 96 (13.3) | 0.019 |
| Acute nephritis | 5 (7.4) | 26 (3.6) | 0.12 |
| Nephrosis | 3 (4.4) | 13 (1.8) | 0.15 |
| Others | 3 (4.4) | 64 (8.9) | 0.15 |
| Year of initial renal biopsy | | | |
| 1994–1995 | 15 (22.1) | 151 (21.3) | |
| 1992–1993 | 25 (36.8) | 168 (23.7) | |
| 1990–1991 | 7 (10.3) | 132 (18.6) | |
| 1988–1989 | 8 (11.8) | 102 (14.4) | |
| 1987 or before | 13 (19.1) | 157 (22.1) | 0.20 |
| Systolic blood pressure (mmHg) | 120 (110–138) | 120 (110–130) | 0.21 |
| Diastolic blood pressure (mmHg) | 74 (68–80) | 70 (62–80) | 0.21 |
| Proteinuria | | | |
| (–), (±) | 6 (9.4) | 286 (41.9) | |
| (+) | 12 (18.8) | 195 (28.6) | |
| (++) | 22 (34.4) | 137 (20.1) | |
| (+++) | 24 (37.5) | 65 (9.5) | <0.001 |
| Haematuria, red blood cells/high-power field | | | |
| None | 6 (9.1) | 182 (26.5) | |
| 1–29 | 49 (74.2) | 388 (56.4) | |
| ≥30 | 11 (16.7) | 118 (17.2) | 0.002 |
| Serum total protein (g/dL) | 6.8 (6.3–7.1) | 7.1 (6.8–7.4) | <0.001 |
| Serum albumin (g/dL) | 4.0 (3.7–4.4) | 4.3 (4.1–4.6) | <0.001 |
| Glomerular filtration rate (mL/min/1.73 m ²) | 78.9 (68.8–97.5) | 80.4 (69.1–95.3) | 0.33 |
| Histological grade of initial renal biopsy | | | |
| Grade I | 10 (15.6) | 190 (28.3) | |
| Grade II | 21 (32.8) | 257 (38.2) | |
| Grade III | 28 (43.8) | 197 (29.3) | |
| Grade IV | 5 (7.8) | 28 (4.2) | 0.002 |

Values are expressed as number (percentage) or median (interquartile range).

baseline serum creatinine levels were excluded from the 2450 patients tracked from 1995. Furthermore, 880 patients with a baseline GFR of 60 mL/min/1.73 m² or less, 491 patients with missing serum creatinine data during the latter half of the follow-up period and 122 patients aged <13 years were also excluded. The remaining 790 patients were included in the current analysis. The median follow-up period of these patients was 119.5 months [interquartile range (IQR), 89–122].

Table 1 summarized demographic and clinical characteristics and baseline laboratory data according to the presence or absence of deterioration in renal function. A total of 68 patients (8.6%) lapsed into substantial renal deterioration, including 23 patients with chronic haemodialysis. Two patients had a doubling of serum creatinine with the maximum value still in the normal range and were classified into the stable renal function group. Because we included patients who reached the endpoint irrespective of its point of time, the follow-up period of the progressive disease group was shorter than that of the stable disease group. Patients who visited the doctors because of macrohaematuria showed a better renal

outcome. Severe proteinuria, mild haematuria, hypoproteinaemia, hypoalbuminaemia and high histopathological grade at renal biopsy were related to deterioration in renal function.

Development of the decision tree model

Figure 1 demonstrates the final tree model that has the smallest Gini index and the largest area under the ROC curve for predicting renal deterioration among 17 candidate models. Of the 14 variables evaluated, the decision tree induction algorithm identified the amount of proteinuria as the best discriminator between patients with and without deterioration in renal function within 10 years of follow-up. Among those patients with severe proteinuria, the best predictor of renal deterioration was serum albumin levels. On the other hand, the presence of mild haematuria was the best predictor of renal deterioration among those without severe proteinuria. The serum total protein levels, diastolic blood pressure and histological grade were selected as the third tier of the stratification for patients with mild proteinuria and mild haematuria, severe proteinuria

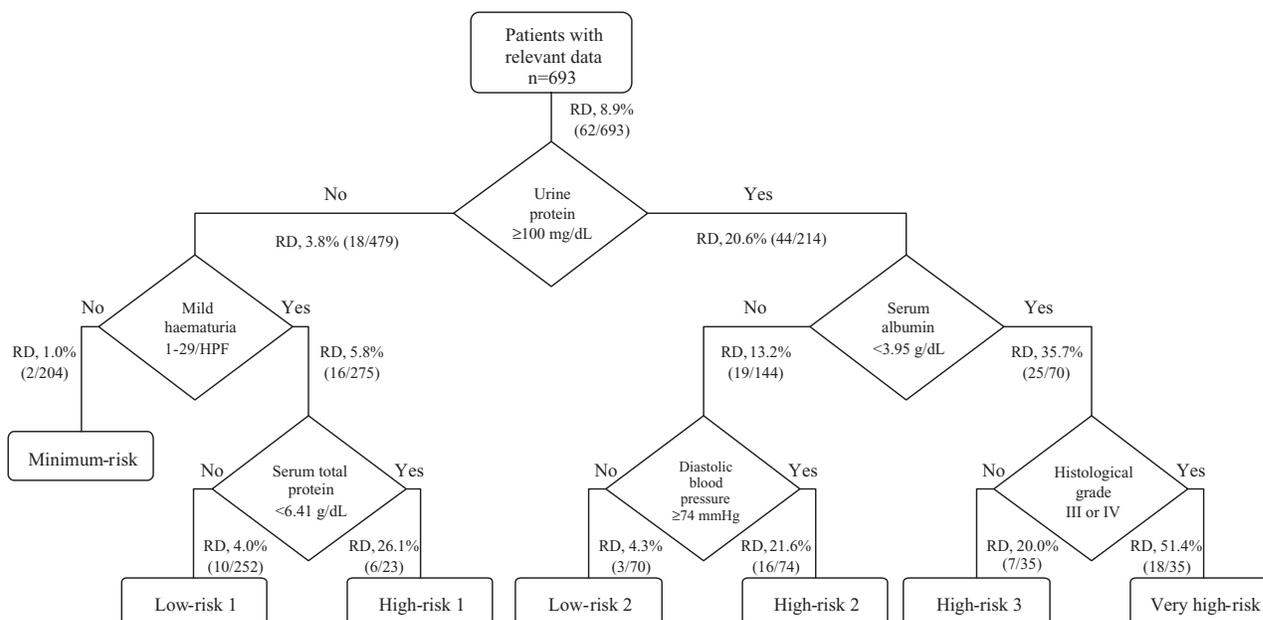


Fig. 1. Final decision tree model. RD denotes subsequently developing renal deterioration.

and normal range of serum albumin and severe proteinuria and hypoalbuminaemia, respectively.

The final tree (Figure 1) has branch points that permit patient stratification into seven risk groups: minimum risk [urine protein <100 mg/dL and the absence of mild haematuria (1–29 red blood cells/high-power field)], low risk 1 (urine protein <100 mg/dL, the presence of mild haematuria and serum total protein ≥6.41 g/dL), low risk 2 (urine protein ≥100 mg/dL, serum albumin ≥3.95 g/dL and diastolic blood pressure <74 mmHg), high risk 1 (urine protein <100 mg/dL, the presence of mild haematuria and serum total protein <6.41 g/dL), high risk 2 (urine protein ≥100 mg/dL, serum albumin ≥3.95 g/dL and diastolic blood pressure ≥74 mmHg), high risk 3 (urine protein ≥100 mg/dL, serum albumin <3.95 g/dL and histological grade I or II) and very high risk (urine protein ≥100 mg/dL, serum albumin <3.95 g/dL and histological grade III or IV). Actual incidences of substantial renal deterioration were 1.0% (2 of 204 patients), 4.0% (10 of 252), 4.3% (3 of 70), 26.1% (6 of 23), 21.6% (16 of 74), 20.0% (7 of 35) and 51.4% (18 of 35) for the minimum-risk, low-risk 1, low-risk 2, high-risk 1, high-risk 2, high-risk 3 and very high-risk groups, respectively.

Confining the analysis to the patients with 24-h urinary protein excretion data ($n = 283$), proteinuria of 0.69 g/day or more was placed in the first tier and hypoalbuminaemia in the second tier in most of the models with different construction settings. Then, data of this subgroup were applied to the final model constructed for the entire dataset replacing dipstick proteinuria of 100 mg/dL with 24-h protein excretion of 0.69 g/day. The model could similarly stratify the patients according to the risk of renal deterioration: actual incidences of substantial renal deterioration were 0% (0 of 72 patients), 4.0% (4 of 100), 4.8% (1 of 21), 25.0% (1 of 4), 14.3% (4 of 28), 15.8% (3 of 19) and 52.9%

Table 2. Risk of substantial deterioration in renal function: comparison between risk groups

| Risk group analysis | Odds ratio (95% CI) | P-value |
|---------------------|---------------------|---------|
| Minimum versus | | |
| low | 4.2 (0.94–19.0) | 0.059 |
| high | 28.4 (6.7–121.5) | <0.001 |
| very high | 106.9 (22.9–500.1) | <0.001 |
| Low versus | | |
| high | 6.7 (3.4–13.4) | <0.001 |
| very high | 25.2 (10.6–59.7) | <0.001 |
| High versus | | |
| very high | 3.8 (1.7–8.2) | 0.001 |

(9 of 17) for the minimum-risk, low-risk 1, low-risk 2, high-risk 1, high-risk 2, high-risk 3 and very high-risk groups, respectively.

Evaluation of the decision tree model

The area under the ROC curve of the decision tree model was 0.830 (95% CI, 0.777–0.883). We merged the low-risk 1 and 2 groups and high-risk 1, 2 and 3 groups because their absolute frequency of renal deterioration was similar (combined incidence, 4.0 and 22.0% in the low- and high-risk groups, respectively). The OR of renal deterioration between the very high- and minimum-risk groups reached 106.9 (95% CI, 22.9–500.1). Discrimination in deterioration risk was almost significant between any two of the risk groups (Table 2).

By virtue of the 5-fold cross-validation, these six variables, especially the amount of proteinuria and the serum albumin levels, were placed on a high tier in most of the models, indicating the robustness of the model. The

median value of the area under the ROC curve in the bootstrap sample, the apparent performance, was 0.837 (IQR, 0.821–0.852) and that in the original sample with the deterioration risk evaluated in the bootstrap sample, the test performance, was 0.827 (IQR, 0.825–0.828). The mean value of the optimism, the difference between these performances, was 0.013 [standard deviation (SD), 0.025]. Then, the internally validated performance was estimated at 0.824 (SD, 0.023), which was close to the performance in the original entire dataset (0.830).

Comparison with logistic regression model

Multivariable logistic regression identified the amount of proteinuria, serum albumin levels and the presence of mild haematuria as significant predictors of deterioration in renal function. Compared with no or trace proteinuria, mild, moderate and severe proteinuria were at greater risks of renal deterioration [ORs, 2.8 (95% CI, 0.96–8.2), 6.8 (2.5–18.6) and 14.4 (5.1–40.9), respectively]. ORs of serum albumin <4.0 g/dL and the presence of mild haematuria (1–29 red blood cells/high-power field) were 3.1 (95% CI, 1.7–5.6) and 2.3 (95% CI, 1.2–4.3), respectively. The addition of 11 other predictors did not meaningfully increase the accuracy of this model. The area under the ROC curve of the logistic regression model was 0.808 (95% CI, 0.754–0.861), which was comparable to that of the decision tree model (0.830).

Discussion

In order to facilitate clinical decision making for IgAN patients in busy clinical settings, clinicians need a practical and user-friendly tool that would rapidly and accurately estimate the individual's long-term renal outcome. The present study proposes a novel risk stratification scheme to identify patients with IgAN who are at risk of substantial deterioration in renal function during 10 years after beginning follow-up using six basic clinical data, the severity of proteinuria, serum albumin levels, mild haematuria, histological grade of renal biopsy, diastolic blood pressure and serum total protein, obtained from routine examination for IgAN. Among the patients whose overall incidence of substantial renal deterioration was 8.9%, our decision tree model can discriminate the risk from 1.0% to 51.4%. It had a high validity because the internally validated performance estimated by the bootstrap procedure was close to the performance in the original entire dataset, and its accuracy was somewhat better than that of the logistic regression model.

The amount of proteinuria was one of the strongest predictors of renal outcome in IgAN patients in many previous studies [5]. Semi-quantitative evaluation, which was not recommended to quantify the amount of urinary protein because of its urine concentration dependence [16], was used in our main analysis because 24-h protein excretion was not measured at baseline for two-thirds of the patients followed. However, the subanalysis including only patients with 24-h urinary protein excretion data yielded almost the

same performance of the decision tree model, indicating the utility of spot urine in the prediction of renal outcome.

Our decision tree model placed histopathological grade in the third tier under substantial proteinuria and hypoalbuminaemia. This agrees with a suggestion by Bartosik *et al.* [17] that clinical features, such as blood pressure and severity of urinary protein excretion, appear to be stronger prognostic indicators than histological findings. Even though many histopathological classifications have been proposed from different regions so far, no satisfying discriminators were found and the debate continues. Even the most widely adopted grading systems have several problems: severity of tubulointerstitial changes are not classified with a clear definition, active and chronic lesions are not interpreted separately and the priority among each element such as cellular proliferation, glomerulosclerosis, crescents and tubulointerstitial damage is not mentioned [18,19]. Additionally, reproducibility and interobserver reliability have not been evaluated for most of the classifications. Standardization of the histopathological findings will facilitate mutual understanding between nephrologists and pathologists in different regions, resulting in the appropriate use of the grading systems based on the scientific evidence in the clinical settings.

Some potential limitations of the current analysis must be acknowledged. Firstly, since information about treatment was not obtained at baseline, we could not evaluate the effects of treatment on the prognosis of IgAN. Secondly, we had to exclude 491 patients because they did not have serum creatinine data during the latter half of the follow-up period, resulting in substantial loss of power. In order to construct an easily understandable prediction tool, we adopted a decision tree induction algorithm that cannot handle censored cases. Thirdly, because only Japanese patients were included in the current analysis, applicability of this prediction model to other populations was not verified. Therefore, additional validation studies with different patient populations are warranted. Nonetheless, the current classification tree analysis of the nationwide follow-up data of IgAN has created a simple, robust, and highly discriminative tool to predict progression of the disease.

In summary, in biopsy-proven IgAN patients without substantial impairment of renal function, the risk of deterioration in renal function can be quickly estimated using clinical information routinely examined for IgAN patients. IgAN patients can be readily stratified into groups at minimum, low, high and very high risk for renal deterioration during 10 years of follow-up, with the risks ranging from 1.0% to 51.4%. The accuracy of these estimates is comparable to that from the logistic regression model. This decision tree model is a promising and useful prediction tool in clinical settings.

Acknowledgements. The authors express their sincere appreciation to the physicians who participated in this study. This study was supported in part by Grant-in-Aid for the Research Group on Progressive Renal Diseases and the Research Committee on the Epidemiology of Intractable Diseases from the Ministry of Health, Labor and Welfare.

Conflict of interest statement. Seven-year follow-up data from this cohort have already been published in *Nephrology Dialysis Transplantation*, October, 2006.

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Received for publication: 17.2.08

Accepted in revised form: 7.10.08

Nephrol Dial Transplant (2009) 24: 1247–1252

doi: 10.1093/ndt/gfn586

Advance Access publication 21 October 2008

Complement deposition in renal histopathology of patients with ANCA-associated pauci-immune glomerulonephritis

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Abstract

Background. The pathogenesis of ANCA-associated pauci-immune glomerulonephritis has not been fully elucidated. Several studies had suggested that complement deposition could be detected in renal histopathology. The current study investigated the clinical and pathological significance of complement deposition in renal histopathology of patients with ANCA-associated pauci-immune glomerulonephritis.

Methods. Renal biopsy specimens from 112 patients with ANCA-associated pauci-immune glomerulonephritis were

investigated using direct immunofluorescence, light and electron microscopy. For direct immunofluorescence, IgG, IgA, IgM, C3c and C1q staining on fresh frozen renal tissue were routinely performed immediately after a renal biopsy. Complement deposition was defined as the presence of C3c or C1q for at least 1+ in a 0–4+ scale. Clinical and histopathological data between patients with and without complement deposition were compared.

Results. In direct immunofluorescence microscopy, C3c and C1q could be detected in glomerular capillary wall and/or mesangium in the specimens of 37/112 (33.0%), 7/112 (6.3%) patients, respectively. Compared with patients without C3c deposition, patients with C3c deposition had a higher level of urinary protein ($P < 0.01$) and poorer initial renal function ($P < 0.05$).

Conclusion. Complement deposition was not rare in renal histopathology of human ANCA-associated pauci-immune

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