IgA nephropathy: prognostic classification of end-stage renal failure

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Abstract

Background. As yet, no clinical or morphological prognostic classification of IgA nephropathy (IgAN) has been generally accepted. The objective of our study was to quantify the risk of developing end-stage renal failure (ESRF) in IgAN.

Methods. We report a prospective longitudinal study of 210 patients with IgAN confirmed by biopsy between 1987 and 1991. Thirty-two (15.2%) patients were lost to follow-up. Mean follow-up after renal biopsy was 5.6 (SD = 2.6) years. The variables included age, gender, illnesses prior to discovery of IgAN, clinical features at IgAN discovery, 24-h proteinuria, serum creatinine, IgA level, and antihypertensive drugs taken at the time of renal biopsy. Sixty-six renal biopsies were classified by light-microscopy according to Lee’s morphological classification. The end-point was ESRF. Survival was analysed by a backward and forward stepwise procedure using the Cox model. The most accurate determination of relative risk was obtained by assessing collinearity of the variables.

Results. Thirty-three patients (15.7%) (31 men) developed ESRF. The five univariately significant variables: gender, gross haematuria, 24-h proteinuria (24-P), serum creatinine (SC), and antihypertensive treatment, were candidates for multivariate analysis. The final model used SC (≤100, 100–150, >150 μmol/l), 24-P (<1, ≥1 g/day) and gender (female vs male) as independent variables (relative risk and 95% confidence interval were 3.5 (2.1, 5.9) for SC; 5.1 (1.9, 13.6) for 24-P; and 3.5 (0.9, 15) for gender). These estimates were used to construct a prognostic classification of ESRF for men with IgAN: stage 1 (SC ≤150 μmol/l and 24-P <1 g/day), stage 2 (SC >150 μmol/l and 24-P <1 g/day) or (SC ≤150 μmol/l and 24-P ≥1 g/day)); stage 3 (SC >150 μmol/l and 24-P ≥1 g/day). The ESRF-free survival was estimated with Kaplan–Meier analysis. It was 98.5% for stage 1, 86.6% for stage 2, 21.3% for stage 3 (P <0.001), 7 years after histological diagnosis.

Conclusions. These classifications identify groups at high risk of ESRF. Therapeutic studies should focus been on these groups.

Key words: end-stage renal failure; IgA nephropathy; prognostic classification

Introduction

IgA nephropathy (IgAN) is the most frequent primitive glomerulonephritis [1,2]. Despite 25 years of research into this condition much remains unknown about its pathogenesis and therapy [3,4]. One major problem is that the prognostic evaluation of IgAN is unreliable. Five studies [5–9] have examined prognostic factors using multivariate analysis, but the candidate factors and their prognostic value varied from one study to another [10]. These differences are undoubtedly due to differing epidemiological approaches. All the studies were retrospective, with cohorts constituted over 10 years [5–9]. These studies were not conclusive as they did not avoid recruitment bias, had many missing data, and many patients were lost to follow-up. Also, recommendations for the optimal use of multivariate analyses [11–15] were not always respected.

Two outlines of clinical prognostic classification have been published [5,6], but neither has been generally accepted. A prognostic classification is useful, even if it cannot predict the outcome for individual patients, because it may help evaluate the disease progression and outcome for a group of patients. It may thus assist clinicians to formulate appropriate management plans and identify patients at risk of chronic renal insufficiency. We assembled a prospective, multicentre cohort over a short inclusion time to analyse the prognosis of IgAN and to develop a prognostic classification using multivariate analysis.
Subjects and methods

Study design and follow-up

Patients over 10 years old who had undergone a renal biopsy between January 1987 and December 1991, and who had major IgA deposits in the mesangium of all the glomeruli in the biopsy were included in a prospective, longitudinal, multicentre study. Any patient suffering from Henoch–Schönlein purpura, lupus erythematosus, or cirrhosis was excluded. Almost all the nephrologists and pathologists practising in eastern France (20 Nephrology units) who take and examine renal biopsies took part in this study. Hence, almost all cases of IgAN in this geographical area were included [2]. Inclusion and follow-up clinical data were collected by the nephrologists who performed the biopsy (see Appendix). The time origin was defined as the day of the first renal biopsy. The observation period was extended to December 1996.

Baseline predictor variables

Baseline predictor variables included age, gender, illnesses prior to discovery of IgAN (such as infection (upper respiratory, respiratory and others infections), tonsillitis in particular, tonsillectomy) and clinical features at IgAN discovery (gross haematuria, microscopic haematuria, proteinuria, or hypertension). The time between discovery and histological diagnosis was calculated. Systolic and diastolic blood pressure, 24-h proteinuria, serum creatinine, and IgA level were measured at the time of renal biopsy and any antihypertensive drugs taken were recorded. Records of the baseline variables were complete, except for illnesses preceding IgAN for four patients and IgA level in 38 patients.

Since 1989, one of the pathologists (BA) has classified 66 biopsies by light-microscopy using Lee’s classification [16] (I, normal without crescents/segmental lesions (sclerosis, adhesions, necrosis); II, <50% glomeruli showing proliferation of mesangial cells, with or without crescents/segmental lesions in <15% glomeruli; III, >50% glomeruli showing proliferation of mesangial cells, with or without crescents/segmental lesions in <50% glomeruli; IV, as for III, but with crescents/segmental lesions in 50–75% glomeruli; V, as for III, but with crescents/segmental lesions/total glomerular sclerosis in >75% glomeruli).

Outcomes

The end-point of individual follow-up was end-stage renal failure (ESRF) requiring dialysis or renal transplantation. Patients who did not reach the end-point were classified as censored; they were lost to follow-up, died before dialysis or transplantation, or were alive at the end of the observation period. Therefore the entire cohort was included in the analysis.

Statistical analysis

In the Cox model, \( e^{\beta} \) represents the multiplicative contribution of each covariate on the hazard function, where \( \beta \) is the unknown regression coefficient and \( z \) the observed covariate [17]. When absence and presence of a studied factor are coded \( z = 0 \) and \( z = 1 \) respectively, \( e^{\beta} \) is the relative risk induced by the studied factor on the hazard rate without this factor. The capacity of each variable to predict each outcome was tested using the likelihood ratio test, the Wald test, and the score test. Variables that reached the 15% significance level in the univariate analysis were considered first for a backward stepwise multivariate analysis and then for a forward stepwise multivariate analysis (enter and remove limits equal to 0.15 and 0.05 respectively). We attempted to satisfy Harrell’s recommendations [13] of 10 outcome events per independent variable.

The Cox model assumes that the relation between the scaled variable of age, time between discovery and histological diagnosis, systolic and diastolic blood pressure, 24-h proteinuria, serum creatinine, IgA level, and the risk of ESRF is logarithmically linear. To check this assumption, these variables were divided into subclasses according to empirical medians and quartiles from the sample, or common clinical cutpoints (for example \( \geq 3 \) g/day for 24-h proteinuria). Each variable was then encoded into exclusive classes and nested classes and the increase of \( \beta \) from one class to the next was studied. If the increase was regular, a discrete variable with \( k \) categories was used. If the increase was not fairly consistent, it was recoded into two classes [12,13,17].

The Cox model assumes that the magnitude of the risk associated with each prognostic variable remains constant over time [12,13,17]. This assumption has been checked using time-dependent covariates [12,17] and Moreau’s method [12,18]. The follow-up data were divided into subclasses according to empirical medians and quartiles from the sample, i.e. 2.3, 5.4 and 7.2 years.

We defined a score for each patient as the component of the log failure rate which does not change with time (i.e. \( z^\beta \) in Cox’s notation). Based on the histogram of these scores, patients were split into three stages [19]. ESRF-free survival rate was plotted over time for each stage using the Kaplan–Meier method. Differences in ESRF-free survival between stages were tested with log-rank statistics.

The 66 patients graded according to Lee’s classification were not significantly different from the other 144 patients in terms of age, gender, duration of disease before renal biopsy, gross haematuria, microscopic haematuria, systolic and diastolic blood pressure, 24-h proteinuria, IgA level, and serum creatinine. Thus this grouped data was treated as a representative sample of the entire cohort, using which we attempted to graphically validate Lee’s classification.

All analyses were performed using BMDP statistical software [20].

Results

A total of 210 patients satisfied the inclusion criteria; 173 (82.4%) were men. The mean age was 36.2 years (median 35.1; range 10–76.7). One hundred and twenty-six patients (60%) had had an infection preceding IgAN discovery, and 73 (35%) had tonsillitis. Of these, 21 (10%) patients underwent tonsillectomy before biopsy and 28 (13%) after biopsy. At IgAN discovery, 89 (42%) patients had gross haematuria, 168 (80%) microscopic haematuria, 160 (76%) proteinuria, and 64 (31%) hypertension. The mean time between discovery and histological diagnosis was 45.9 months (median 12.3; range 0.06–440). At the time of renal biopsy, the mean systolic blood pressure was 136.1 mmHg (median 130; range 100–230), and diastolic blood pressure was 81.6 mmHg (median 80;
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The mean 24-h proteinuria was 1.6 g (median 1; range 0–12). The mean serum creatinine was 146.8 μmol/l (median 97.5; range 44–1327). The mean IgA level was 3.5 g/l (median 3.2; range 0.6–9). In terms of antihypertensive treatments, 152 (72.4%) patients were not treated, 29 (13.9%) were taking one drug, 23 (10.9%) two drugs, and six (2.8%) three drugs.

Thirty-three patients (31 men) reached the endpoint, i.e. ESRF, for a total of 33 (15.7%) events. Ten patients died before ESRF. The mean follow-up time of the 167 remaining patients was 5.6 (SD = 2.6) years after the histological diagnosis. Thirty-two patients were lost to follow-up 2.5 (SD = 1.9) years after renal biopsy. These 32 patients had an average age of 27.7 (SD = 11.9) years at histological diagnosis and had a mean serum creatinine of 88 (SD = 23.5) μmol/l.

The results of the univariate analysis are shown in Table 1. The underlying assumption of log linearity was checked only for serum creatinine, divided into three classes (≤100, 100/150, >150 μmol/l) and for systolic blood pressure, divided into three classes (≤120, 120/150, >150 mmHg). Other continuous variables were divided into two classes.

Hypertension at discovery, systolic and diastolic blood pressure and the antihypertensive treatment were all highly correlated. Proteinuria at discovery and 24-h proteinuria at histological diagnosis were also closely correlated. Thus the quantitative risk estimated for each variable may be imprecise in multivariate analyses [13].

After the backward stepwise analysis, only gender, gross haematuria, 24-h proteinuria, serum creatinine and antihypertensive treatment were included in the forward multivariate analysis. The model yields three independent variables, serum creatinine, 24-h proteinuria and gender (Table 2, analysis 1).

Hypertension, as indicated by antihypertensive treatment, was not entered into the model. If antihypertensive treatment and 24-h proteinuria had been the only two candidate variables, they would both have been entered into the model (Table 2, analysis 2). High blood pressure did not predict ESRF, once it has been corrected for serum creatinine at histological diagnosis. This suggests that the concentration of serum creatinine at this time may be the link between high blood pressure and ESRF.

Age, adjusted for blood pressure, did not predict ESRF, suggesting that high blood pressure could be the intervening variable in the link between age and ESRF.

Figure 1 shows the histogram of the scores, calculated using the estimated regression coefficients of serum creatinine, 24-h proteinuria and gender in the analysis 1 (Table 2). A high score indicates an elevated risk of ESRF. The relative risk of ESRF was 3.5 times higher for men than women. Consequently these data were used to define a clinical classification system of ESRF risk for men with IgAN:

- stage 1 (serum creatinine ≤150 μmol/l and 24-h proteinuria <1 g):
- stage 2 ((serum creatinine >150 μmol/l and 24-h proteinuria <1 g) or (serum creatinine ≤150 μmol/l and 24-h proteinuria ≥1 g)):
- stage 3 (serum creatinine >150 μmol/l and 24-h proteinuria ≥1 g).

The probability of ESRF-free survival for men was 98.5% for stage 1, 86.6% for stage 2, and 21.3% for

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**Table 1. Predictors of end-stage renal failure determined using a univariate Cox proportional hazards model**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Coding</th>
<th>Patients within code or interval (n)</th>
<th>Relative risk per unit change</th>
<th>95% confidence interval</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female/male</td>
<td>37/173</td>
<td>3.7</td>
<td>0.9; 15.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;35/≥35 years</td>
<td>105/105</td>
<td>1.3</td>
<td>0.6; 2.5</td>
<td>0.5§</td>
</tr>
<tr>
<td>Infection</td>
<td>Yes/No</td>
<td>126/84</td>
<td>1.3</td>
<td>0.6; 2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Tonsilitis</td>
<td>Yes/No</td>
<td>73/134</td>
<td>1.4</td>
<td>0.7; 3.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>Yes/No</td>
<td>49/157</td>
<td>1.9</td>
<td>0.8; 5</td>
<td>0.2</td>
</tr>
<tr>
<td>Gross haematuria</td>
<td>Yes/No</td>
<td>89/121</td>
<td>2.5</td>
<td>1.1; 5.5</td>
<td>0.02§</td>
</tr>
<tr>
<td>Microscopic haematuria</td>
<td>No/Yes</td>
<td>168/42</td>
<td>1.1</td>
<td>0.5; 2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>No/Yes</td>
<td>50/160</td>
<td>9.5</td>
<td>1.3; 68.7</td>
<td>0.02§</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No/Yes</td>
<td>146/64</td>
<td>2.9</td>
<td>1.5; 5.7</td>
<td>&lt;0.003§</td>
</tr>
<tr>
<td>Duration between discovery and</td>
<td>Long/short</td>
<td>101/109</td>
<td>1.1</td>
<td>0.6; 2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>histological diagnosis</td>
<td>&gt;12/≤12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤120/120</td>
<td>82/87/41</td>
<td>2.6</td>
<td>1.6; 4.1</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>140/150</td>
<td>82/87/41</td>
<td>2.6</td>
<td>1.6; 4.1</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>24-h proteinuria</td>
<td>≤1/≥1 g</td>
<td>105/105</td>
<td>8.1</td>
<td>3.1; 21</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>≤100/150&gt;150 μmol/l</td>
<td>109/53/48</td>
<td>4.2</td>
<td>2.6; 7</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>IgA level</td>
<td>≤3.25/3.25 g/l</td>
<td>87/85</td>
<td>1.1</td>
<td>0.5; 2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>No/Yes</td>
<td>152/58</td>
<td>4.7</td>
<td>2.4; 9.4</td>
<td>&lt;0.001§</td>
</tr>
</tbody>
</table>

*The first code has the lower risk of ESRF.

*Peak value of *P* among the *P* of the three tests (likelihood ratio test, Wald test, score test).

§, §§The assumption of proportional hazard function over time is verified with both methods: §§ time-dependent covariate, Moreau’s method; § time-dependent covariate method only.
Table 2. Results of the forward stepwise multivariate analyses

<table>
<thead>
<tr>
<th>Analysis 1*</th>
<th>Candidate variable to enter the model</th>
<th>$\chi^2$ at the last step</th>
<th>Relative risk per unit change of the independent variable entering the model and the 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(210 patients)</td>
<td>Serum creatinine</td>
<td>28.4</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>24-h proteinuria</td>
<td>14.6</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>4.4</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Antihypertensive treatment</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gross hematuria</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Analysis 2**</td>
<td>24-h proteinuria</td>
<td>19.7</td>
<td>6.4</td>
</tr>
<tr>
<td>(210 patients)</td>
<td>Antihypertensive treatment</td>
<td>11.3</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*Analysis 1 is the main multivariate analysis with the five univariately significant variables.

**Analysis 2 shows that hypertension is a predictor of ESRF when serum creatinine at histological diagnosis is not taken into account.

Fig. 1. Histogram of the scores of the 210 patients. A high score indicates an elevated risk of end-stage renal failure. For example, a female with 220 μmol/l (>150 μmol/l) of serum creatinine and 2.2 g (>1 g) of 24-h proteinuria, had a score of $(1.27*0)+(1.25*2)+(1.63*1)=4.13$.

Fig. 2. Stage 3 ($P<0.001$) 7 years after histological diagnosis. As only two women had ESRF, we did not develop a classification system for women.

Thirteen (19.6%, 13 men) of the 66 patients classified according to Lee had ESRF after a mean follow-up period of 4.3 (SD: 2.4) years. Figure 3 shows the graphical validation of Lee’s classification on these patients ($P<0.001$).

Discussion

It is difficult to assess the prognosis of IgAN because of the very long time between histological diagnosis and renal death [14]. The use of chronic renal insufficiency as an end-point would overestimate the survival time, because the exact time at which serum creatinine exceeds 150–200 μmol/l is still difficult to measure in renal disease. The impaired renal function may remain stable for a long time and then suddenly deteriorate, leading to ESRF within a few months. While the exact date of ESRF is easier to determine, taking ESRF as the end-point would underestimate the number of unfavourable events when follow-up is short. Nevertheless, like most authors [5,6,8], we have used ESRF as the end-point.

Some results [9] are difficult to explain, because of the many missing data (18%), the small number of events (<10%), the lack of information on the number of variables included in the final model and the value of relative risk. This study identifies renal function at last follow-up, expressed as the serum urea concentration, as a risk factor for ESRF. Incorporating information collected during the follow-up period into the
Fig. 2. Kidney survival for men according to the stages derived from the Cox model. SC, serum creatinine; 24-P, 24-h proteinuria at renal biopsy. After 6 years of follow-up, the number of men at risk is indicated in parentheses.

Fig. 3. Graphical validation of Lee's classification. After 3 years of follow-up, the number of patients at risk is indicated in parentheses.
analysis could bias the results of an analysis toward the correct qualitative conclusion about the direction of an association [15].

The four other retrospective studies published to date [5–8] all indicated that severe proteinuria was the main variable affecting prognosis. When it was included in the variables used in the regression, the presence of renal insufficiency at diagnosis [6,8] was also associated with an unfavourable prognosis. Our results are consistent with this, as a model with these two variables fits our data. Other variables, such as the absence of gross haematuria [6], initial hypertension [6,7], and HLA B 35 antigen [7] have been considered as indicating a poor prognosis. The results of our study indicate that high blood pressure may account for the increase in serum creatinine at histological diagnosis. This elevated serum creatinine appears to be a more powerful prognostic factor for ESRF than high blood pressure.

In our study, 31 (17.9%) men vs 2 (5.4%) women developed ESRF. We found male gender to be an independent predictor of ESRF in the multiple Cox’s regression analysis, in contrast with results from earlier multivariate studies [5–10]. But this is consistent with two univariate studies [16,21], in which respectively 16.1% and 15% men vs 4.1% and 7% women respectively developed ESRF. These results are also consistent with those of a recent epidemiological survey of primary glomerular diseases (PGD) in a French region which showed that male gender was a risk factor for poor renal prognosis of PGD [1].

The statistical association between the potential prognostic factors means that the results of univariate analysis should be interpreted with caution. Only certain variables found to be significant in univariate analysis should be selected for multivariate analysis to obtain a good estimate of relative risk. The published studies have not always fulfilled this criterion. In some cases multivariate analyses were performed with 11 or even 18 variables [5,7]. These studies, which retain all the variables as candidates to enter the model give interesting results, but are subject to errors due to collinearity [13]. Somewhat surprisingly, renal function at diagnosis was not a variable selected in two studies [5,7]. Consequently, in these studies, the prognostic value of the histological data must be analysed with caution, as there is a correlation between the degree of renal insufficiency and the severity of histological lesions. We included only the five variables that appeared to summarize all the information, and which were not correlated (gender, gross haematuria, 24-h proteinuria, antihypertensive treatment, and serum creatinine) in our stepwise analysis to limit these sources of bias.

In a preliminary study [22], we showed that subjects over the age of 50 were more commonly hypertensive at the onset of IgAN. At histological diagnosis, systolic blood pressure was significantly higher, but not diastolic blood pressure in these subjects over age 50. The glomerular and tubulointerstitial lesions were no more severe in the older patients and only endarteritis was more common in these patients. However, this difference seems to be due to age rather than IgAN. The present study suggests that the effect of age on renal function is due to the higher blood pressure of older subjects. Thus, we did not include age in the multivariate analysis to avoid minimizing the effect on prognosis of hypertension.

Accurate estimation of relative risk, with acceptable confidence intervals, depends directly on the methods used. A prospective study such as this has several advantages, including a complete data set at inclusion, a representative sample of all the various clinical forms of the disorder and few cases lost to follow-up.

For IgAN, the constancy of the risk over time, an important assumption of the Cox model, have been considered to be uncertain [7]. We used two statistical methods [17,18] and the agreement between the results indicates that the effect on prognosis of 24-h proteinuria, serum creatinine, and gender were constant throughout the study.

The overall estimates of relative risk from serum creatinine at diagnosis, 24-h proteinuria at histological diagnosis and gender appear to be even closer, as the confidence intervals were small. Three distinct groups were identified on the basis of severity. Stage 1 contained men (46% of the total) with virtually no risk of developing ESRF within 8 years. There was 1 in 5 chance of developing ESRF within 8 years in stage 2 (36% of all the men), while in stage 3 the male patient (18%) had almost a 1 in 4 chance of developing ESRF within 1 year and a greater than 2 in 3 chance of developing ESRF within 5 years. Although the development of ESRF differs greatly between patients with IgAN, the progression of IgAN is often described as being uniform, in terms of the yearly decrease in glomerular filtration rate [3], or by the percentage of patients developing renal failure per year of follow-up [4,10]. Our group of male patients could be divided into at least three groups, each with a different rate of disease progression. This classification requires validation by other independent studies, but it does identify clinical indicators of prognosis at 5 years not previously published.

Except in one study [23], each prognostic [5,7,8,16] and therapeutic [24–26] study defines histological progression differently. There is no international consensus for a morphological classification. Lee [16] found that glomerular lesions were all that was required for prognosis, whereas others also included tubulointerstitial [5,7,8] and vascular lesions [7]. Our data show that Lee’s classification [16] is valid, at least for a short follow-up period. It is easy to use and accurately predicts prognosis for cases of IgAN. However, it may be necessary to regroup certain grades (Figure 3).

Various trials of potential IgAN therapies have been conducted [23–26]. Most treatments have not proved effective in controlled trials. Recent trials have been more encouraging despite conflicting results [24,25]. Many features of these studies should be reviewed [3], particularly the lack of stratification for proteinuria and renal function. This study provides a clinical
Appendix

L'Association des Néphrologues de l’Est (The Eastern France Association of Nephrologists) includes the following investigators:


References


Received for publication: 24 9 96
Accepted in revised form: 24 7 97