Histological grading of IgA nephropathy predicting renal outcome: revisiting H. S. Lee’s glomerular grading system

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Abstract

Background. The glomerular grading system is useful to compare biopsy specimens and to predict the natural course of disease in IgA nephropathy (IgAN), although no grading system can be perfect.

Methods. H. S. Lee’s grading system for IgAN was refined as follows: grade I, normal or focal mesangial cell proliferation; grade II, diffuse mesangial cell proliferation, or <25% of glomeruli with crescent (Cr)/segmental sclerosis (SS)/global sclerosis (GS); grade III, 25–49% of glomeruli with Cr/SS/GS; grade IV, 50–75% of glomeruli with Cr/SS/GS; grade V, >75% of glomeruli with Cr/SS/GS. This refined H. S. Lee grading system was then tested for clinical relevance on 187 patients with IgAN followed up for an average of 6.5 years (minimum, 3 years). In the survival analysis, a modified primary end-point (progressive renal disease) was used.

Results. The glomerular grades were significantly related to hypertension, serum creatinine levels and the amounts of proteinuria at time of biopsy. By univariate analysis, glomerular grades, hypertension, renal insufficiency and significant proteinuria (≥1 g/day) were significantly associated with progressive renal disease. By multivariate analysis using the Cox regression model, glomerular grades, renal insufficiency and significant proteinuria were independent prognostic factors for progressive renal disease. At the end of follow-up, glomerular grades were significantly related to serum creatinine levels, amounts of proteinuria, hypertension and progressive renal disease.

Conclusions. These findings indicate that the refined H. S. Lee grading system for IgAN is useful in assessing the patients’ clinical outcome and is sufficiently simple and easy to reproduce as to be universally applicable in prognostic work.

Keywords: H. S. Lee’s glomerular grading system; IgA nephropathy; prognosis; progressive renal disease; renal survival

Introduction

IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide and in Korea [1,2]. Fifteen to 40% of the patients, though initially reported with a benign prognosis, eventually progress to end-stage renal disease (ESRD) [3–9].

A number of reports have emphasized the prognostic value of glomerular changes with focal segmental glomerulosclerosis [6,9,10–14], crescents [6,9,15] or diffuse mesangial cell proliferation [5,16,17], and tubulointerstitial changes [3,9,12,13] in IgAN. To compare biopsy specimens and to predict renal outcome, a semi-quantitative scoring system [4,7] and glomerular grading system [1,14,16–18] were proposed, though no grading system can be perfect and the debate on histological evaluation continues. Thus, it is imperative to reach a consensus on grading systems that is universally applicable for prognostic work.

Benjamin H. Spargo from the University of Chicago first applied Meadow’s grading system for Henoch–Schönlein nephritis [19] to IgAN [16]. As shown in Table 1, the criteria for S. M. K. Lee’s scoring system [16] and glomerular grading system [1,14,16–18] were proposed, though no grading system can be perfect and the debate on histological evaluation continues. Thus, it is imperative to reach a consensus on grading systems that is universally applicable for prognostic work.

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was defined in its grades II–V [16]. Thus, B. H. Spargo devised the new grading system specifying the percentage of the glomeruli affected by the segmental lesions and/or global sclerosis in each grade for his routine renal biopsy work, leading H. S. Lee et al. [1,2] to adopt his grading system for Korean patients with IgAN (Table 1). There was a strong correlation between H. S. Lee’s grade IV and V lesions and poor prognosis in patients with IgAN [1]. Although S. M. K. Lee [20] claimed that H. S. Lee et al. [1,2] directly applied the grading system of S. M. K. Lee et al. [16] in their clinopathological study, the two grading systems are basically different, as shown in Table 1.

Meadow et al. [19], S. M. K. Lee et al. [16] and Haas [17] regarded the extent and degree of mesangial cell proliferation as an important prognosticator in their grading system. However, determining the degree of mesangial cell proliferation at the light microscopy level is subjective and, therefore, a disector technique is required for obtaining unbiased estimates of the cell number. Furthermore, mesangial hypercellularity could be reversible [21] and does not indicate the severity of tissue damage [18], nor does it correlate with renal failure or proteinuria [7]. In contrast, crescents and segmental sclerosis represent the most severe glomerular lesions associated with an actively necrotizing and/or chronic progressive trajectory in most glomerular diseases [6,9,15].

Because histological criteria for H. S. Lee’s grading system [1] also included extent, though not degree, of mesangial cell proliferation, H. S. Lee’s grade III encompasses a wide variety of lesions showing 1–49% (<50%) of the glomeruli affected by segmental sclerosis/crescents together with diffuse mesangial proliferative glomerulonephritis (Table 1). Furthermore, in grade IV and V lesions, the increase in mesangial matrix is more prominent than cell proliferation, suggesting that mesangial hyperplasia is not an essential parameter for the diagnosis of these two grades. In addition, the number of patients diagnosed with H. S. Lee’s grade I is almost negligible. Thus, it has become necessary to refine H. S. Lee’s glomerular grading system, particularly in specifying the percentage of the glomeruli affected by crescents/segmental sclerosis in grades II and III, with less emphasis on mesangial cell proliferation.

The present study addressed this issue and tested refinements made to H. S. Lee’s grading system for clinical relevance on 187 patients with IgAN with follow-up intervals ranging from 3 to 18 years.

### Subjects and methods

#### Patients

The diagnosis of IgAN was made at the Seoul National University Hospital between 1984 and 1998 on 453 patients. All of them had >20 glomeruli in their renal biopsies by serial sectioning. IgAN diagnosis was based on immunofluorescence microscopy showing mesangial IgA deposition as the predominant or co-dominant immunoglobulin, and on the lack of clinical or laboratory evidence of systemic lupus erythematosus, Henoch–Schönlein purpura or liver cirrhosis.

Of these, 187 patients were followed up for >3 years and formed the basis of this study. For each patient, data were collected concerning age, sex, date of clinical onset, blood pressure, blood urea nitrogen, serum creatinine concentration, urinalysis, 24-h urinary protein quantification, and creatinine clearance at the time of biopsy and at follow-up.

#### Histological grading

We slightly modified H. S. Lee’s glomerular grading system [1] by specifically defining the percentage of glomeruli affected by crescents/segmental sclerosis/global sclerosis in grades II–V, and neglecting the degree of mesangial cell proliferation.
in grades III–V. In cases without segmental sclerosis or crescents, patients showing focal proliferative glomerulonephritis were diagnosed as having grade I, while those with diffuse mesangial proliferative glomerulonephritis were diagnosed as grade II (Table 1). Table 1 summarizes the criteria for histological grading proposed by Meadow et al. [19], S. M. K. Lee et al. [16] and H. S. Lee et al. [1].

Three renal pathologists read 50 biopsies, which were selected randomly from the materials to perform kappa analysis in order to assess inter-observer variability.

We also tested the schema of S. M. K. Lee et al. [16] and Haas [17] for clinical relevance on our 187 patients to evaluate whether the refined H. S. Lee grading system is better than those that are in use.

Data analysis

SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL) was used for data analysis. All numerical data were expressed as mean±SD. The differences in means between groups were compared by independent samples t-tests or one-way analysis of variance (ANOVA). Post hoc analysis was performed by the Bonferroni method. \( \chi^2 \) analysis was used when comparing frequencies between the groups.

In the survival analysis, Narita et al. [22] defined the primary end-point (progressive renal disease) as the date when the serum creatinine level was double that at the time of diagnosis, or when the patients underwent their first haemodialysis. However, not all patients who double their serum creatinine values become haemodialysis-dependent and, therefore, we looked at the slope of serum creatinine values over time in these patients and excluded those showing relatively static serum creatinine levels from the progressive renal disease group in the survival analysis. Renal survival data were analysed using Kaplan–Meier survival functions, with significance of differences between the patient groups determined using both the G-rho family of log-rank test procedures for survival data and Cox regression analysis. Kaplan–Meier survival curves and Cox proportional hazard regression models were used to analyse the time course from renal biopsy to primary end-points. Glomerular grades I and II, as well as grades III and IV were combined to evaluate the significance of clinicopathological variables as predictors of renal survival using the Cox proportional hazard model. The covariates, which were statistically significant in the univariate analysis, were then included in the multivariate analysis, and the effects of these covariates were expressed by a hazard ratio. A value of \( P < 0.05 \) was considered to indicate statistical significance.

Results

Clinical data in relation to glomerular grading at time of biopsy

The 187 patients consisted of 104 males and 83 females. Ages at time of biopsy ranged from 3 to 67 years with a mean age of 30±15 (SD) years; 47 patients (25%) were under 15 years of age. One hundred and ten patients (59%) had significant proteinuria of ≥1 g per day, of whom 25 (13%) showed nephrotic range proteinuria of ≥3.5 g per day. Renal insufficiency, defined as a serum creatinine level of >1.5 mg/dl, was observed in 30 cases (16%). Hypertension, defined as blood pressure >140/90 mmHg, was found in 44 cases (24%). Of the 77 patients with proteinuria <1 g per day, 10 were treated with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II (AII) receptor blocker to control hypertension, while 67 received no treatment. Of the remaining 110 patients, 81 received an ACE inhibitor or AII receptor blocker and/or low dose steroids, and 21 cases having nephrotic syndrome were treated with an ACE inhibitor and steroids or even azathioprine.

The distribution in glomerular grades of the 187 patients was: grade I, 13 (7%); grade II, 73 (39%); grade III, 66 (35%); grade IV, 22 (12%); and grade V, 13 (7%). Values of kappa between renal pathologist A and B ranged from 0.61 to 0.70, those between renal pathologist A and C from 0.68 to 0.73, and those between renal pathologist B and C from 0.59 to 0.65. Clinical features at the time of biopsy for each of the glomerular grades of IgAN are summarized in Table 2. Younger age was significantly related to lower histological grades (\( P < 0.001 \)). The frequency of hypertension, serum creatinine levels and amounts of proteinuria increased as the histological grade became higher (\( P < 0.001 \)). There was also an inverse relationship between creatinine clearance and histological grades (\( P < 0.001 \)). No significant difference with respect to sex

Table 2. Clinical data of patients with IgA nephropathy in relation to glomerular grades at the time of biopsy

<table>
<thead>
<tr>
<th>Glomerular grades</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>( P^1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n ) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>21±15</td>
<td>24±15</td>
<td>35±14</td>
<td>40±11</td>
<td>31±11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>9:4</td>
<td>43:30</td>
<td>35:31</td>
<td>10:12</td>
<td>7:6</td>
<td>NS²</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.86±0.18</td>
<td>0.85±0.23</td>
<td>1.12±0.43</td>
<td>1.40±0.50</td>
<td>4.71±4.72</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>104.0±26.9</td>
<td>99.9±40.2</td>
<td>83.1±31.6</td>
<td>66.7±27.7</td>
<td>43.0±34.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Proteinuria (g/24h)</td>
<td>0.7±1.1</td>
<td>1.6±2.3</td>
<td>1.7±1.3</td>
<td>2.1±1.8</td>
<td>5.5±3.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Haematuria [n (%)]</td>
<td>10 (77)</td>
<td>67 (92)</td>
<td>60 (91)</td>
<td>18 (82)</td>
<td>13 (100)</td>
<td>NS³</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>1 (8)</td>
<td>6 (8)</td>
<td>18 (27)</td>
<td>10 (46)</td>
<td>9 (69)</td>
<td>&lt;0.001⁴</td>
</tr>
</tbody>
</table>

Values represent mean±SD. NS, not significant.

1 Data are compared with *ANOVA or \( \chi^2 \) test.
and frequency of haematuria was observed between different grades (Table 2).

**Clinical outcome in relation to histological and clinical parameters**

The follow-up of 187 patients ranged from 3 to 18 years after biopsy, with a mean of 6.5 ± 3.6 (SD) years. One hundred and twenty patients (64%) were followed up for >5 years.

During the follow-up period, 14 patients (7%) showed ESRD, of whom 11 underwent haemodialysis, two received renal transplants and one patient died. Another 19 patients doubled their serum creatinine level as compared with that at the time of diagnosis. Of these, 13 patients showed a progressive increase in serum creatinine values, whereas six retained relatively static values (Figure 1). Thus, 27 patients (14%) with either ESRD or progressive deterioration of renal function were grouped as having progressive renal disease in the survival analysis.

By univariate analysis, hypertension (log-rank test, \( P < 0.0001 \)), renal insufficiency at time of biopsy (\( P < 0.0001 \)), proteinuria ≥1 g/day (\( P = 0.0043 \)) and glomerular grading (\( P < 0.0001 \)) were significant risk factors for poor renal survival (Figure 2). Age and sex were not correlated with renal survival.

According to multivariate analysis using the Cox proportional hazard regression model, glomerular grades, renal insufficiency and significant proteinuria were independent prognostic factors for renal survival. The hazard ratio for progressive renal disease was 35.46 [95% confidence interval (CI), 6.271–200.445; \( P < 0.001 \)] for histological grade V, 5.55 (95% CI, 2.172–14.206; \( P = 0.001 \)) for renal insufficiency, and 3.29 (95% CI, 1.121–9.663; \( P = 0.030 \)) for proteinuria ≥1 g/day (Table 3).

At the end of follow-up, renal insufficiency was observed in 54 patients (28%), hypertension in 83 (44%), significant proteinuria in 95 (51%) and ESRD in 14 (7%) of the 187 patients. Mean values of serum creatinine and proteinuria, and the frequency of hypertension and progressive renal disease at the end of follow-up were significantly increased in accordance with increased glomerular grades (\( P < 0.001 \)) (Table 4).

**Analysis of patients using the S. M. K. Lee and Haas grading systems**

The distribution in glomerular grades of the 187 patients using the S. M. K. Lee system was: grade I, seven (4%); grade II, 19 (10%); grade III, 152 (81%); grade IV, nine (5%); and grade V, 0. That using the Haas system was: grade I, 12 (6%); grade II, 10 (5%); grade III, 54 (29%); grade IV, 61 (33%); and grade V, 50 (27%). For these characteristics, only grade V of the Haas system had an association with progressive renal disease by univariate analysis (\( P < 0.001 \)). None of the other grades had an association with the progression rate.

**Discussion**

In the present study, we analysed 187 patients with IgAN with a mean follow-up of 6.5 years utilizing a refined version of H. S. Lee’s glomerular grading system and confirmed the utility thereof in assessing the clinical outcome and present state of the disease.
Standard renal survival plots create only two categories, i.e. renal failure (ESRD) or renal survival. The use of this end-point identifies only a small number of patients with IgAN with advanced renal disease rather than reflecting the progression rate [23]. Indeed, only a small number of patients showed ESRD in this study, too. Thus, we modified the primary end-point proposed by Narita et al. [22] for use in survival analysis, and found that the refined H. S. Lee glomerular grades, hypertension, renal insufficiency and significant proteinuria were significantly associated with progressive renal disease by univariate analysis. In agreement with previous reports [3–7,9,17], renal insufficiency and significant proteinuria were found to be strong risk factors even at multivariate analysis in the present study. However, only a small minority of patients with IgAN had renal impairment at presentation, and its presence does little to predict the rate of progression, a factor of great importance for the individual at risk [23]. Although proteinuria and hypertension at the time of biopsy are important

Table 3. Significance of clinicopathological variables as predictors of renal survival using the Cox proportional hazard model

<table>
<thead>
<tr>
<th>Variables</th>
<th>P-value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I + II</td>
<td>&lt;0.001</td>
<td>3.158</td>
<td>0.656–15.200</td>
</tr>
<tr>
<td>III + IV</td>
<td>0.151</td>
<td>3.158</td>
<td>0.656–15.200</td>
</tr>
<tr>
<td>V</td>
<td>&lt;0.001</td>
<td>35.455</td>
<td>6.271–200.445</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>0.001</td>
<td>5.554</td>
<td>2.172–14.206</td>
</tr>
<tr>
<td>Proteinuria ≥1 g/day</td>
<td>0.030</td>
<td>3.291</td>
<td>1.121–9.663</td>
</tr>
</tbody>
</table>

Fig. 2. (A) Kaplan–Meier renal survival curve to compare histological grading (grade I, 13 cases; grade II, 73 cases; grade III, 66 cases; grade IV, 22 cases; grade V, 13 cases). The survival rate is significantly higher in patients with lower glomerular grades (P < 0.0001). (B) Renal survival curve to compare hypertensive (n = 44) vs normotensive patients (n = 143) at the time of biopsy. The survival rate is significantly higher in patients without hypertension (P = 0.0001). (C) Renal survival curve to compare patients with renal insufficiency (n = 30) vs those without (n = 157) at the time of biopsy. The survival rate is significantly higher in patients without renal insufficiency (P < 0.0001). (D) Renal survival curve to compare patients with proteinuria ≥1 g/day (n = 110) vs those with proteinuria <1 g/day (n = 77) at the time of biopsy. The survival rate is significantly higher in patients with proteinuria <1 g/day (P = 0.0043).
prognostic indicators in the great majority of cases of chronic renal disease, these factors probably account for no more than 30% of the total risk of progression in IgAN [23,24]. Indeed, for the majority of patients, clinical prognosticators are weak on a case-by-case basis, suggesting that additional information gained from sequential clinical data during follow-up might enhance the quality of prognostication [23].

We observed that refinements made to H. S. Lee’s glomerular grading could be a powerful independent prognostic factor for progressive renal disease by multivariate analysis. Furthermore, higher glomerular grades were significantly related to the occurrence of hypertension, larger amounts of proteinuria and higher levels of serum creatinine at the end of follow-up. Grade V, in particular, was most significantly associated with loss of renal function and progression, as shown in Tables 3 and 4 and Figure 2A. In our previous study on IgAN using H. S. Lee’s glomerular grading system, patients with histological grades IV and V also exhibited progressive renal disease [1], corroborating the present observations.

In the present study, higher glomerular grades were significantly associated with hypertension, higher serum creatinine levels and larger amounts of proteinuria at the time of biopsy. These findings are in agreement with our previous reports on IgAN [1], suggesting that H. S. Lee’s glomerular grading may best be indicative of the present state of the disease. We also observed that younger age significantly correlated with lower glomerular grades, supporting the notion that older age at the time of discovery may be a marker of poor prognosis [9].

An advantage of the grading or lumped system in IgAN is its simplicity and ease of application in large multi-centre studies, while its disadvantage is the lack of flexibility in interpretation and the chance of missing the important isolated pathological changes [12]. Ideally, the glomerular grading system should simplify a wide range of histopathological features for IgAN by classifying it according to the severity of the lesion, so that higher grades can represent increasing severity and/or chronicity of the disease. Although some authors regarded mesangial cell proliferation as an important prognosticator in their grading system [16,17], determining the degree of mesangial cell proliferation is subjective. Furthermore, mesangial hypercellularity could be reversible [21] and does not necessarily indicate poor renal outcome [7,18]. In contrast, glomerular crescents and segmental sclerosis have long been regarded as the most severe glomerular lesions associated with an actively necrotizing and/or chronic progressive course of the disease [6,9,15].

As mentioned earlier, H. S. Lee’s grade III [1] encompasses a wide variety of lesions. This problem can be solved in the refined H. S. Lee’s grading system by subdividing the cases with 25–49% glomeruli affected by crescents/segmental and/or global sclerosis into grade III, and those with <25% glomeruli affected by the lesion into grade II regardless of the extent or degree of mesangial cell proliferation. In addition, patients without segmental sclerosis or crescents can be diagnosed as having either grade I or grade II according to the extent of mesangial hyperplasia. Furthermore, grade IV and V lesions can also be diagnosed according to the percentage of glomeruli affected by crescents/segmental and/or global sclerosis irrespective of the degree or extent of mesangial hyperplasia. Assessment of the percentage of glomeruli with segmental/global sclerosis or crescents is relatively simple and objective. Indeed, the refined H. S. Lee’s grading is simple and easy to reproduce with little inter-observer variability as assessed by kappa analysis. Thus, the refined H. S. Lee grading system for IgAN proposed here seems to satisfy the requirements for an ideal glomerular grading system.

In 1997, Haas [17] presented a new grading system, which showed that higher grades represented more severe mesangial cell proliferation, whereas lower grades contained lesions of focal segmental glomerulosclerosis. When the Haas and S. M. K. Lee systems were tested for clinical relevance on our own patients, only grade V of the Haas system had an association with progressive renal disease by univariate analysis. None of the other grades had an association with progressive renal disease by univariate analysis. In support of our findings, the schema of S. M. K. Lee grading system is better than those that are in use. In contrast, Haas and/or Lee did not attain reproducibility in retaining prognostic significance when tested by other researchers [13,23]. In 2000, To et al. [14] reported another glomerular grading system, which was based solely on the amounts of mesangial matrix or extent

Table 4. Clinical data of patients at the end of follow-up in relation to glomerular grades

<table>
<thead>
<tr>
<th>Glomerular grades</th>
<th>I (n = 13)</th>
<th>II (n = 73)</th>
<th>III (n = 66)</th>
<th>IV (n = 22)</th>
<th>V (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>0.85 ± 0.19</td>
<td>1.11 ± 1.43</td>
<td>2.24 ± 2.77</td>
<td>2.38 ± 1.66</td>
<td>9.92 ± 5.81** &lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>0.18 ± 0.21</td>
<td>0.59 ± 0.94</td>
<td>1.04 ± 1.09</td>
<td>1.13 ± 0.95</td>
<td>3.30 ± 4.02*** &lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>2 (15)</td>
<td>22 (30)</td>
<td>33 (50)</td>
<td>13 (59)</td>
<td>13 (100)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Progressive renal disease [n (%)]</td>
<td>0</td>
<td>2 (3)</td>
<td>9 (14)</td>
<td>5 (23)</td>
<td>11 (65)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are compared with *ANOVA or #χ² test.

**p < 0.05 vs other groups by Bonferroni’s post hoc analysis.
of segmental sclerosis in each glomerulus. This system, however, cannot be used routinely in renal biopsy work because a morphometric study is required to measure mesangial volume, even though an increase in mesangial matrix points to a poor renal outcome.

The semi-quantitative scoring system for IgAN contained tubulointerstitial and vascular lesions in addition to glomerular lesions [3,4,7,11,13]. In the present study, these lesions were not assessed for comparison with glomerular lesions. While there is obvious merit in counting each of these different components of the renal biopsy, changes in different components are highly inter-related [1,4,14], and the complexity of this approach limits its potential for widespread use [17]. Nonetheless, tubulointerstitial injury directly correlates with renal outcome in IgAN [3,9,12,13], similar to most other glomerular diseases. In particular, a report suggests that tubular lesions are strongly correlated with chronic renal failure in IgAN [13]. In this regard, interstitial volume density obtained by the point counting method could be used as a prognosticator in IgAN in parallel with glomerular grading system.

In summary, the refined H. S. Lee grading system provides important prognostic information and stands as an independent morphological predictor of renal outcome. Thus, a refined H. S. Lee grading system for IgAN is useful in assessing patients’ clinical outcome and is sufficiently simple and easy to reproduce as to be universally applied for prognostic work.

Conflict of interest statement. None declared.

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Received for publication: 2.7.04
Accepted in revised form: 10.11.04