Secondary Publication: Clinical Grade of IgA Nephropathy

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Review

Secondary Publication: Clinical Grade of IgA Nephropathy

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During this half a century since immunoglobulin A (IgA) nephropathy was firstly reported in 1968, several clinical and histological grading systems to predict the prognosis have been reported. In Japan, since the first version of clinical guideline for IgA nephropathy was established in 1995, it was revised in 2014 to the third version which was the grading system based on both clinical and histological risk factors. In this report, we have shown the details and evaluation of clinical grading system of that Japanese guideline, and also shown the previous reported clinical grading system.
This report is secondary publication of previous our review report "Nippon Rinsho 77: 643-650, 2019".

Key Words: IgA nephropathy, clinical grading system, risk factors, proteinuria, estimated glomerular filtration rate

Introduction

Immunoglobulin A (IgA) nephropathy as a disease entity was first reported by Berger et al. in France 50 years ago, in 1968.[1] While it was initially considered as a disease with a good prognosis, it came to be recognized in the 1990's that it, in fact, has a poor long-term prognosis, with 30% of IgA nephropathy progress to end-stage renal disease (ESRD) within 20 years from its onset.[2,3] Various treatment strategies for IgA nephropathy have been reported for avoiding ESRD, including treatment with steroids and/or renin-angiotensin system (RAS) inhibitors and tonsillectomy. In addition, attempts to identify the risk factors for ESRD from among various clinicopathological variables have been made, which have led to the proposal that the disease be classified in accordance with the clinical/pathological severity, based on such risk factors.

In Japan, such classification is now included in the guidelines for the management of IgA nephropathy in clinical practice. In this paper, we review and discuss the validity of clinical severity classification of this disease adopted in the current IgA nephropathy management guideline (3rd edition),[4] and also outline other reports published until date concerning the classification of the severity of IgA nephropathy on the basis of the laboratory test data.

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Table 1a Prognostic criteria for IgA nephropathy.

Classification		
Patients with IgA nephropathy are clinically divided into the following four groups at the time of renal biopsy. It should be noted, however,that the prognostic group as determined at the time of renal biopsy may change during the clinical course of the disease.		
1	Good prognosis group	Dialysis will probably never be required.
2	Relatively good prognosis group	The likelihood of dialysis is relatively low.
3	Relatively poor prognosis group	Dialysis is likely to be required within 5-20 years.
4	Poor prognosis group	The possibility of dialysis within 5 years is high.
The purpose is to define prognostic criteria to aid the selection of an appropriate treatment in individual patients with IgA nephropathy.		
Adapted from reference 6 Jpn J Nephrol 2002.		

Table 1b Clinical parameters uses as prognostic criteria in addition to renal biopsy findings.

Parameters	Relatively poor prognosis group	Poor prognosis group
Blood pressure* (mmHg)	140-160/85-95 (persistent)	>160/95 (persistent)
Serum creatinine* (mg/dL)	1.3-1.5	≥1.6
Creatinine clearance (mL/min)	50-80	<50
Urinary protein (g/day)	0.5-2.0 (persistent)	≥2.0 (persistent)

Values for blood pressure and serum creatinine are different in children.
Adapted from reference 6 Jpn J Nephrol 2002.

Clinical Severity Classification of IgA Nephropathy in Japan

1. Changes in the clinical severity classifications in management guidelines

Many of the severity grading systems proposed until date from Japan, Asia, Europe and the USA are based on the pathological findings, or a combination of the clinical and pathological findings. There is hardly any severity classification based solely on the laboratory test data. This is probably because not only the clinical features, but also the pathological features of this condition are diverse and very important in determining the severity level of IgA nephropathy. In Japan, the first edition of the IgA nephropathy management guideline was published in 1995 by the Progressive Nephropathy Research Group within the framework of the Ministry of Health and Welfare Specific Disease Research Program.[5] Later, in 2002, the 2nd edition of the same guideline was published.[6] The revision at that time only consisted of addition of several sentences to the 1st edition (partial revision on the basis of new evidence collected after publication of the 1st edition). In this edition (2nd edition) of the management guideline, "diagnostic criteria for IgA nephropathy," "criteria for predicting the prognosis of IgA nephropathy," and "guidelines for the treatment of IgA nephropathy" were proposed. Of these, the "criteria for predicting the prognosis of IgA nephropathy" represents the so-called severity classification, according to which patients with IgA nephropathy were divided into four groups: the good prognosis group, relatively good prognosis group, relatively poor prognosis group, and poor prognosis group (**Table 1a**). This classification was based on the glomerular findings and other histopathological findings related to the renal tubules, interstitium and vessels. Clinical findings were used only as reference criteria, "serving as an auxiliary means for predicting the prognosis in cases showing a tendency towards aggravation of the blood pressure, serum creatinine level, creatinine clearance and urinary protein excretion level" (**Table 1b**). Thus, the tendency towards a lower significance attached to clinical findings relative to the histopathological findings in the 1st edition of the guideline continued into the 2nd edition.

Publication of the 3rd edition (2011), however, involved a full-scale revision of the guideline.[4] This latest revision was based on the recognition that the clinical findings had been given less importance in the previous

two editions and that underestimation of the importance of clinical findings may be problematic, as in clinical practice, there may be cases showing discrepancies between the pathological findings and clinical findings (for example, it is unknown to what extent importance should be attached to clinical findings in cases with a high urinary protein excretion level despite only mild histopathological changes of the renal tissue). As a result, establishment of a classification giving equal weightage to the clinical and histopathological findings was proposed. We believe that this latest classification is more reliable, especially in view of the fact that the clinical findings of IgA nephropathy at presentation are diverse (e.g., proteinuria, hematuria, renal function impairment).

2. IgA nephropathy management guideline —3rd edition—

The 3rd edition of the IgA nephropathy management guideline was prepared on the basis of the results of logistic regression analysis performed to determine the relationship between the histopathological/laboratory findings and the renal prognosis in a total of 287 cases selected from 16 facilities nationwide between February 1980 and January 2002. The selected patients included: (1) patients from whom 10 or more glomeruli could be collected by renal biopsy; (2) patients who could be followed up for 5 years or more after renal biopsy or patients who had begun to receive dialysis; (3) patients whose treatment details were well known (regardless of the nature of treatment). The detailed data used for preparation of the 3rd edition have also been reported by Okonogi et al.[7]

After the exclusion of 17 cases with incomplete data, analysis of the remaining 270 patients revealed that 48 of the 270 patients progressed to ESRD. Two-group comparison between ESRD group and renal survival group and univariate analysis identified high urinary protein excretion, low estimated glomerular filtration rate (eGFR), high serum uric acid level, advanced age, male gender and presence of hypertension as factors significantly associated with ESRD. However, there was no influence of hematuria (which was prevalent at equivalent rates in the two groups), whose importance has been increasingly recognized in recent years. The multivariate logistic regression analysis, performed using the above mentioned risk factors identified as significant by the univariate analysis plus several additional factors, including hematuria, history of steroid therapy (significance found in univariate analysis), history of treatment with RAS inhibitors (no significance found), revealed that each 1 g/day increase of the urinary protein excretion resulted in a 1.61-fold elevation of the risk (odds ratio) for initiation of dialysis (95% confidence interval (CI) 1.20-2.17; $p = 0.002$), and each 10 mL/min/1.73 m^2 increase of the eGFR resulted in a 0.64-fold decrease of the odds ratio for the initiation of dialysis (95% CI 0.49-0.84; $p = 0.01$); thus, these two parameters were identified as factors significantly associated with ESRD. However, hypertension, which had been included as one of the reference factors in the 2nd edition was not adopted as a criterion in the laboratory test data-based severity classification in the 3rd edition of the guideline, because it was found to show no association with the prognosis (odds ratio 1.28, 95% CI 0.45-3.66; $p = 0.646$). Furthermore, according to the receiver operating characteristic (ROC) analysis, the areas under curve (AUCs) of the ROC curve for proteinuria and eGFR were reported to be 0.774 and 0.777, respectively. In addition, on the basis of an earlier report by Okonogi et al.,[8] urinary protein excretion 0.5 g/day and eGFR 60 mL/min/1.73 m^2 were set as the cutoff levels through application of these parameters to the cutoff determining equation, namely, threshold score $(-1.86) = 0.722 + 0.364 \times$ urinary protein $- 0.046 \times$ eGFR. The patients could be divided into four classes of disease severity based on these parameters: Class I (urinary protein excretion <0.5 g/day and eGFR ≤60 mL/min/1.73 m^2), Class II (urinary protein excretion <0.5 g/day and eGFR >60 mL/min/1.73 m^2), Class III (urinary protein excretion ≥0.5 g/day and eGFR ≤60 mL/min/1.73 m^2), and Class IV (urinary protein excretion ≥0.5 g/day and eGFR >60 mL/min/1.73 m^2). Because only 7 cases were included in Class II, and there were no cases of renal death, Class II was combined with Class I to form a new class (C-Grade I). Thus, the 4-category classification was changed to a 3-category classification (C-Grades I, II and III, **Table 2**, left). When this classification was applied, rather reasonable results were obtained, with the odds ratio for renal death in the C-Grade II group being 6.4-fold higher, and that in the C-Grade III group being 42.5-fold higher than the ratio in the C-Grade I group (95% CI 1.4-28.4; p =

Table 2 Clinical grade of IgA nephropathy.

Clinical grade	Proteinuria (g/day)	eGFR (mL/min/1.73 m^2)	Odds ratio	95% CI	p-value
C-Grade I	<0.5	-	1	–	–
C-Grade II	0.5≤	60≤	6.4	1.4-28.4	0.015
C-Grade III		<60	42.5	9.6-189	<0.001

CI, confidence interval.

Based on reference 4 Jpn J Nephrol 2011 and reference 7 Clin Exp Nephrol 2019.

Table 3 The risk of progression to ESRD according to the combination of the clinical grade and the histological grade.

Clinical grade \ Histological grade	H-Grade I	H-Grade II	H-Grade III+IV
C-Grade I	1/72 (1.4%) OR: 1	0/10 (0%) OR: 0	1/5 (20%) OR: 17.8
C-Grade II	7/64 (11%) OR: 8.7	6/41 (15%) OR: 12.2	3/18 (17%) OR: 14.2
C-Grade III	2/5 (40%) OR: 47.3	6/21 (29%) OR: 28.4	22/34 (65%) OR: 130

The number of patients progressed to ESRD/total number of patients (%).

OR, odds ratio vs. H-Grade I/C-Grade I.

Adapted from reference 4 Jpn J Nephrol 2011.

0.015, and 9.6-189, $p < 0.001$) (**Table 2**, right). This result has been explained as an outcome of addition of the histological severity (H-Grade) to the classification in the 3rd edition of the IgA nephropathy management guideline (**Table 3**). Also, in the aforementioned study by Okonogi et al.,[8] who reported the equation for calculating the cutoff levels of urinary protein excretion and eGFR for the 3rd edition (urinary protein excretion 0.5 g/day and eGFR 60 mL/min/1.73 m^2), the authors analyzed the data of 116 patients who had been followed up for a maximum of 25 years, adopting the renal biopsy-based glomerulus count and the minimum follow-up period, similar to the entry criteria for the 3rd edition; the univariate analysis identified only urinary protein excretion and eGFR as the risk factors for renal death among all the clinical variables analyzed (urinary protein excretion, eGFR, serum uric acid, age, gender, presence/absence of hypertension and hematuria). Also, in the multivariate analysis performed using these clinical variables plus the history of steroid therapy and history of treatment with RAS inhibitors, only urinary protein excretion and eGFR were identified as significant risk factors for renal death. The same investigators additionally reported that in the ROC curve analysis, the AUC for urinary protein excretion was 0.752 and that for eGFR was 0.799, and that the combination of the two factors was more useful for prediction of the prognosis (AUC: 0.815). Furthermore, they performed a two-graph ROC (TG-ROC) analysis and set the threshold score (sensitivity approximately equal to specificity) at −1.86, followed by calculation of the cutoff values using the aforementioned equation. They reported cutoff levels of 1.0 g/day for urinary protein excretion and 64 mL/min/1.73 m^2 for the eGFR, and classified the severity of the disease in the patients according to the laboratory abnormalities as follows: Grade I: urinary protein excretion <1.0 g/day and eGFR ≥64 mL/min/1.73 m^2; Grade II: urinary protein excretion <1.0 g/day and eGFR <64 mL/min/1.73 m^2; Grade III: urinary protein excretion ≥1.0 g/day and eGFR ≥64 mL/min/1.73 m^2 and Grade IV: urinary protein excretion ≥1.0 g/day and eGFR <64 mL/min/1.73 m^2. However, similar to the case in the cohort examined for preparing the 3rd edition of the guideline, the number of Grade II patients was small (12 cases) and there were no cases of renal death in this group. For this reason, Grade II was combined with Grade I for the evaluation. In this latter evaluation, additionally adopting the effects of steroid therapy and treatment with RAS inhibitors, the odds ratio for renal death in the Grade III patients cases was 9.6-fold (95% CI 1.0-89.4; $p = 0.048$), and that in the Grade IV patients was 43.9-fold (95% CI 4.7-407, $p = 0.001$), as compared to that in the Grade I + II patients. Thus, despite some dif-

ferences in the data recorded, this evaluation also demonstrated the validity of the laboratory test data-based severity classification established using urinary protein excretion and eGFR.

Other Severity Classifications Based on Laboratory Data

Many papers have been published concerning various risk factors for the progression of IgA nephropathy, but few have summarized these factors into a scoring system and reported the validity of such a scoring system for determining the disease severity. As mentioned above, the reports often took into account the histological severity, and according to our literature search, only the reports by Magistroni et al.[9] and Xie et al.[10] have adopted solely the laboratory test data-based severity classification, other than our report. This section will focus on these reports and pay attention only to the laboratory test data-based severity classification among the classification systems based on the clinicopathological severity.

Magistroni et al. conducted a multivariate analysis of 237 Caucasians with IgA nephropathy in Italy, and identified four factors (Cr at renal biopsy, urinary protein excretion, age and gender) as being risk factors for ESRD, and proposed a clinical prognostic index (CPI). Because Cr is most closely associated with ESRD, this CPI assigns a score 2 for Cr >1.4 mg/dL, 1 to urinary protein excretion >1.0 g/day, 1 to the presence of hypertension, and 1 to age >30 years (total score 5). They divided the patients into a low CPI group (CPI score ≤ 2) and high CPI group (score ≥ 3), reporting that the 10-year survival rate was significantly higher in the low CPI group (91.7%) than in the high CPI group (31.1%) ($p < 0.001$). They conducted evaluation of its validity in another district of Italy, in 73 Caucasians, and reported that the 10-year survival duration was significantly higher in the low CPI group (80.5%) than in the high CPI group (31.1%) ($p = 0.007$).

Xie et al. in China conducted multivariate analysis using a stepwise Cox proportional hazards model in 619 patients with IgA nephropathy, which identified four factors, i.e., eGFR, hemoglobin (Hb), serum albumin (Alb) and systolic blood pressure at the time of renal biopsy as factors associated with the prognosis. They divided the Risk Score (RS) calculated as $6.932 - 0.039 \times$ eGFR (mL/min/1.73 m^2) $- 0.23 \times$ Hb (g/dL) $- 0.762 \times$ Alb (g/dL) $+ 0.016 \times$ systolic blood pressure (SBP, mmHg) into three tertiles: 1st tertile: RS <−0.89, 2nd tertile: −0.89-0.99, and 3rd tertile: >0.99. When the odds ratio for ESRD in the 1st tertile was deemed to be 1, the ratio was 15.3 in the 2nd tertile (95% CI 2.0-115.0) and 79.8 in the 3rd tertile (95% CI: 11.0-580.3), demonstrating that the risk for ESRD increased as the RS increased. It is noteworthy that in the study conducted by Xie et al., urinary protein excretion, which is generally known as a powerful prognostic factor, was not identified as a factor associated with ESRD, because of the presence of Alb, which was correlated inversely with renal death according to the multivariate analysis, and of Hb, which was found as a risk factor associated with IgA nephropathy (lower in IgA nephropathy patients than in healthy individuals and the risk of disease progression rising by 20% with each 1.0 g/dL reduction of the Hb). The AUC of the ROC curve in their study was higher than that reported by Berthoux et al., or later by Goto et al., even though Xie et al. emphasized that these data could be derived from routine laboratory tests and that their results were from a large-scale cohort study involving more than 600 subjects. However, it seems necessary to evaluate its validity in other ethnic groups, etc.

In the severity classification proposed by Berthoux et al.,[11] which additionally took into account the histological findings, the absolute renal risk (ARR) was calculated by simply assigning a score of 1 to each of (1) hypertension (140/90 mm Hg), (2) urinary protein excretion (1 g/day or more), and (3) seriousness level of tissue damage, to yield a total score being 3. They reported the incidence of events (ESRD or mortality) in 332 Caucasian patients with IgA nephropathy in France whose data were analyzed prospectively. The incidence of events at 10 years and 20 years was 2% and 4% in the AAR0 (ultralow risk) group, 2% and 9% in the AAR1 (high-risk) group, 7% and 18 % in AAR2, and 29% and 64% in the AAR3 (ultrahigh risk) group, respectively. The odds ratio analyzed by the COX proportional hazard model, with AAR3 serving as the control group, was 0.28 (95% CI 0.14-0.60; $p < 0.0009$) in the AAR2 group, 0.09 (95% CI 0.03-0.30, $p < 0.0001$) in the AAR1 group, and 0.06 (95% CI 0.02-0.17; $p < 0.0001$) in the AAR0 group, indicating a reduc-

Table 4 (**a**) Scores to estimate the risk of ESRD by demographic and clinical factors (**b**) The estimated 10-year risk of ESRD by total score (**c**) Scores of Norwegian cohort.

(a) Scores to estiate the risk of ESRD

Factors		Score
Gender	Male	6
Age	<30 years	12
Systolic blood pressure (mmHg)	≤130	0
	131-160	4
	>160	11
Urinary protein excretion	(−), (±)	0
	(+)	12
	(++)	21
	(+++)	25
Hematuria	1-29 RBC/HPF	8
Serum albumin	<4.0 g/dL	7
Glomerular filtration rate (mL/min/1.73 m^2)	≥90	0
	60-90	7
	30-60	22
	15-30	42
	<15	66
H-Grade	Grade III or IV	5

(b) estimated 10-year risk of ESRD by total score

Total score	10-year risk (%)
0-26	0-1
27-43	1-5
44-50	5-10
51-58	10-20
59-63	20-30
64-70	30-50
71-75	50-70
76-82	70-90
83-140	90-100

(c) Grading of Norwegian cohort

Group
A
B
C
D
E

Based on reference 13 Nephrol Dial Transplant 2009 and reference 14 Nephrol Dial Transplant 2011.

tion in the incidence of events as the score decreased.

Wakai et al. in Japan prospectively followed 2,269 patients with IgA nephropathy from 97 facilities in Japan for 7 years from 1995 to 2002 and analyzed the risk factors for disease progression.[12] They scored the risk for renal death at 4 years or 7 years using the laboratory test data-based severity classification (gender, age, systolic blood pressure, urinary protein excretion, hematuria, serum total protein and Cr) and the histological severity classification (Japanese IgA Nephropathy Management Guidelines, 2nd edition), and divided the scores into many ranges (from −8 to 116). High scores were assigned to elevation of the serum Cr and urinary protein excretion, which had been found to be strong risk factors in the multivariate analysis (Cr: score 0 for values ≤1.25 mg/dL and 47 for values ≥2.5 mg/dL; proteinuria: score 24 for qualitative assay 3+), while only one-digit lower scores were assigned to gender, age, etc., which had been identified as significant factors only in the univariate analysis. The highest score assigned to the histopathological severity was as low as 9. Thus, their scoring system attached importance to the laboratory test data-based severity classification.

Goto et al. reported a clinicopathological severity classification using data from the same cohort after extending the follow-up period to 10 years, adopting a simpler scoring system (**Table 4a, b**).[13] Unlike the previous classification in which Cr was divided into 47 ranges, the GFR was adopted, values of which were divided into 5 ranges (identical to the number of chronic kidney disease [CKD] stages). At the same time, Alb was adopted instead of serum total protein (which had been divided into 8 ranges), with only 2 ranges (< 4 g/dL or ≥ 4 g/dL). The other scores were also simplified. As a result, the risk for renal death was divided from the previous 100 ranges to only 9 ranges, making this system much easier to use to predict the prognosis. Also with this classification, higher scores were assigned to laboratory test data-based severity as compared to the histological classification, indicating that this classification placed greater emphasis on the laboratory abnormalities. Hematuria was also scored as a risk factor, but it is noteworthy that probably because macroscopic hematuria was found to be associated with a good prognosis, in terms of the urinary red blood cell count, mild hematuria (1-29/high-power field [HPF]) was associated with a poorer prognosis than severe hematuria (30/HPF or higher) (mild vs. severe hematuria: incidence of renal death: 18.2 vs. 12.3%, odds ratio: 2.83 vs. 1.86). To validate this severity classification, a validation study was conducted in a cohort of 633 Caucasians in Norway, with an follow-up period extended to 20 years.[14] In that study, the results of the multivariate analysis revealed approximately similar results in terms of the influence of various factors, except for gender. The number of sever-

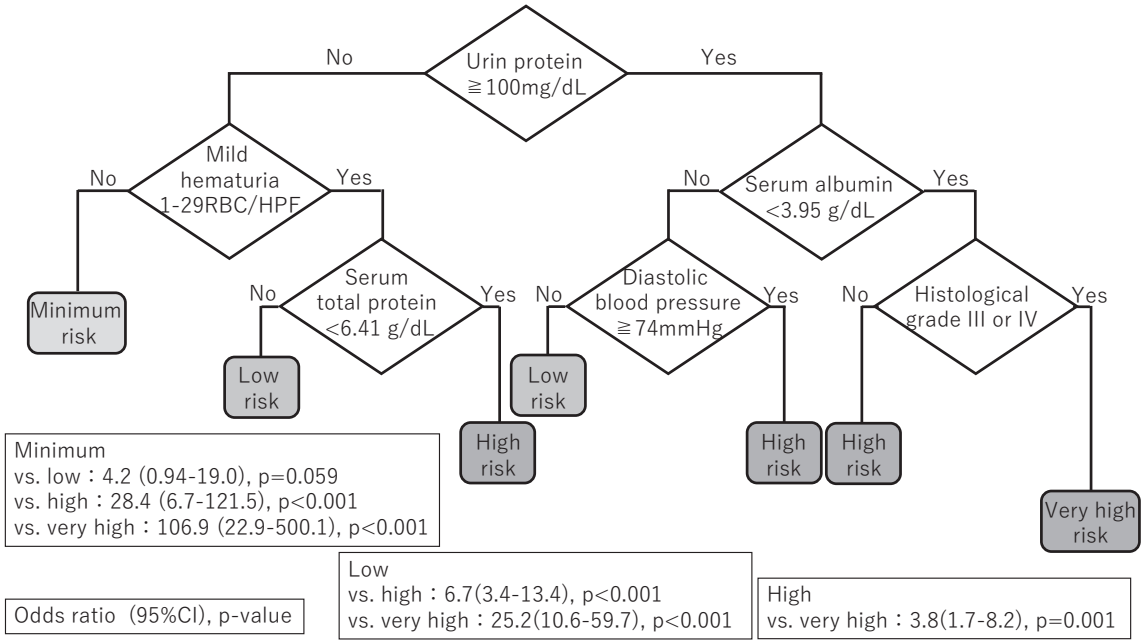

Figure 1 Final decision tree model.
The final tree has branch points that permit patient stratification into seven risk groups. The risk of substantial deterioration in renal function: comparison between risk groups.
Based on reference 15 Nephrol Dial Transplant 2009.

ity levels was reduced from the previous 9 to 5 on the basis of the cumulative renal death rate (**Table 4c**), and the new grades of cumulative renal death rate yielded reasonable results (Group A: 3.9%/20 years; Group B: 14.0%/17.5 years; Group C: 42.3%/17.5 years; Group D: 60.9%/15 years, E: 87.7%/10 years). Furthermore, using the data of the 790 cases aged 13 years or over with preserved renal function (eGFR ≥ 60 mL/min/1.73 m^2) in the aforementioned cohort from 97 facilities in Japan, Goto et al. prepared a decision tree model (**Figure 1**).[15] This decision tree was confined to cases with a favorable eGFR. For this reason, the laboratory test data-based severity classification adopted five factors, including urinary protein excretion (a major factor, known as the strongest prognostic factor), mild hematuria, Alb, serum total protein and diastolic blood pressure, while excluding renal function parameters. With this classification, the severity was finally divided into 4 levels (minimal, low, high and ultrahigh). Histological classification was one of the minor factors in this severity classification, which placed more emphasis on the laboratory test data-based severity.

Conclusion

In this article, we provide an explanation about the laboratory test data-based severity classifications proposed until date. In recent years, risk factors (e.g., urinary protein excretion, hematuria, gradient of eGFR) taking into account the efficacy of initial treatment during the first year after diagnosis have also been reported. However, for selection of the appropriate treatment soon after renal biopsy and for prediction of the prognosis, the severity based on the laboratory test data at the time of renal biopsy seems to be very important, perhaps equivalent to the findings of renal biopsy. In Japan, the 3rd edition of the IgA nephropathy management guideline, revised taking into consideration both of these aspects, has been published recently. Now, a prospective multicenter study involving more than 1,000 cases in Japan is currently under way for reassessing the validity of this type of severity classification. The study is expected to provide further evidence supporting the excellent features of this severity classification.

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Conflicts of Interest: The authors declare that they have no competing interests.

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