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## REFERENCES

1. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. *Semin Nephrol* 2004; **24**: 179–196.
2. Donadio JV, Bergstralh EJ, Grande JP *et al.* Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. *Nephrol Dial Transplant* 2002; **17**: 1197–1203.
3. Ibels LS, Gyory AZ. IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine (Baltimore)* 1994; **73**: 79–102.
4. Nicholls KM, Fairley KF, Dowling JP *et al.* The clinical course of mesangial IgA associated nephropathy in adults. *Q J Med* 1984; **53**: 227–250.
5. Woo KT, Edmondson RP, Wu AY *et al.* The natural history of IgA nephritis in Singapore. *Clin Nephrol* 1986; **25**: 15–21.
6. Reich HN, Troyanov S, Scholey JW *et al.* Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol* 2007; **18**: 3177–3183.
7. Alamartine E, Sabatier JC, Berthoux FC. Comparison of pathological lesions on repeated renal biopsies in 73 patients with primary IgA glomerulonephritis: value of quantitative scoring and approach to final prognosis. *Clin Nephrol* 1990; **34**: 45–51.
8. Radford Jr MG, Donadio Jr JV, Bergstralh EJ *et al.* Predicting renal outcome in IgA nephropathy. *J Am Soc Nephrol* 1997; **8**: 199–207.
9. Katafuchi R, Kiyoshi Y, Oh Y *et al.* Glomerular score as a prognosticator in IgA nephropathy: its usefulness and limitation. *Clin Nephrol* 1998; **49**: 1–8.
10. Churg J, Sobin LH. *Renal Disease, Classification and Atlas of Glomerular Disease*, Tokyo, Igaku-Shoin, 1982.
11. Lee SM, Rao VM, Franklin WA *et al.* IgA nephropathy: morphologic predictors of progressive renal disease. *Hum Pathol* 1982; **13**: 314–322.
12. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. *Am J Kidney Dis* 1997; **29**: 829–842.
13. Wakai K, Kawamura T, Endoh M *et al.* A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. *Nephrol Dial Transplant* 2006; **21**: 2800–2808.
14. Manno C, Strippoli GF, D'Altri C *et al.* A novel simpler histological classification for renal survival in IgA nephropathy: a retrospective study. *Am J Kidney Dis* 2007; **49**: 763–775.
15. Coppo R, Schena FP. IgA nephropathies. In: Davison AM, Ritz E, Cameron JS, Winearls C (eds). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford University Press: Oxford, UK, 2005.
16. Bartosik LP, Lajoie G, Sugar L *et al.* Predicting progression in IgA nephropathy. *Am J Kidney Dis* 2001; **38**: 728–735.
17. Feehally J, Barratt J, Coppo R *et al.* International IgA nephropathy network clinico-pathological classification of IgA nephropathy. *Contrib Nephrol* 2007; **157**: 13–18.
18. Roberts ISD, Cook T, Troyanov S *et al.* The Oxford classification of IgA Nephropathy: Pathology definitions, correlations and reproducibility. *Kidney Int* 2009; (in press).
19. Mina SN, Murphy WM. IgA nephropathy. A comparative study of the clinicopathologic features in children and adults. *Am J Clin Pathol* 1985; **83**: 669–675.
20. Wuhl E, Witte K, Soergel M *et al.* Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. *J Hypertens* 2002; **20**: 1995–2007.
21. Yoshimoto M, Tsukahara H, Saito M *et al.* Evaluation of variability of proteinuria indices. *Pediatr Nephrol* 1990; **4**: 136–139.
22. Work DF, Schwartz GJ. Estimating and measuring glomerular filtration rate in children. *Curr Opin Nephrol Hypertens* 2008; **17**: 320–325.
23. Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130**: 461–470.
24. Shen P, He L, Li Y *et al.* Natural history and prognostic factors of IgA nephropathy presented with isolated microscopic hematuria in Chinese patients. *Nephron Clin Pract* 2007; **106**: c157–c161.
25. Beukhof JR, Ockhuizen T, Fleuren GJ *et al.* Relation between proteinuria and morphology in IgA nephropathy. *Contrib Nephrol* 1984; **40**: 228–235.
26. Abe T, Kida H, Yoshimura M *et al.* Participation of extracapillary lesions (ECL) in progression of IgA nephropathy. *Clin Nephrol* 1986; **25**: 37–41.
27. Nicholls K, Walker RG, Dowling JP *et al.* Malignant' IgA nephropathy. *Am J Kidney Dis* 1985; **5**: 42–46.
28. Johnston PA, Brown JS, Braumholtz DA *et al.* Clinico-pathological correlations and long-term follow-up of 253 United Kingdom patients with IgA nephropathy. A report from the MRC Glomerulonephritis Registry. *Q J Med* 1992; **84**: 619–627.
29. Frimat L, Briancon S, Hestin D *et al.* IgA nephropathy: prognostic classification of end-stage renal failure. L'Association des Nephrologues de l'Est. *Nephrol Dial Transplant* 1997; **12**: 2569–2575.
30. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. *Am J Kidney Dis* 1997; **29**: 526–532.
31. Packham DK, Yan HD, Hewitson TD *et al.* The significance of focal and segmental hyalinosis and sclerosis (FSHS) and nephrotic range proteinuria in IgA nephropathy. *Clin Nephrol* 1996; **46**: 225–229.
32. Armstrong GD. The intraclass correlation as a measure of interrater reliability of subjective judgments. *Nurs Res* 1981; **30**: 314–315, 320A.
33. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159–174.
34. Koch GG, Landis JR, Freeman JL *et al.* A general methodology for the analysis of experiments with repeated measurement of categorical data. *Biometrics* 1977; **33**: 133–158.

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# The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility

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**Pathological classifications in current use for the assessment of glomerular disease have been typically opinion-based and built on the expert assumptions of renal pathologists about lesions historically thought to be relevant to prognosis. Here we develop a unique approach for the pathological classification of a glomerular disease, IgA nephropathy, in which renal pathologists first undertook extensive iterative work to define pathologic variables with acceptable inter-observer reproducibility. Where groups of such features closely correlated, variables were further selected on the basis of least susceptibility to sampling error and ease of scoring in routine practice. This process identified six pathologic variables that could then be used to interrogate prognostic significance independent of the clinical data in IgA nephropathy (described in the accompanying article). These variables were (1) mesangial cellularity score; percentage of glomeruli showing (2) segmental sclerosis, (3) endocapillary hypercellularity, or (4) cellular/fibrocellular crescents; (5) percentage of interstitial fibrosis/tubular atrophy; and finally (6) arteriosclerosis score. Results for interobserver reproducibility of individual pathological features are likely applicable to other glomerulonephritides, but it is not known if the correlations between variables depend on the specific type of glomerular pathobiology. Variables identified in this study withstood rigorous pathology review and statistical testing and we recommend that they become a necessary part of pathology reports for IgA nephropathy. Our methodology, translating a strong evidence-based dataset into a working format, is a model for developing classifications of other types of renal disease.**

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KEYWORDS: glomerulonephritis; IgA nephropathy; Oxford classification; pathology; renal failure

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The histological diagnosis of IgA nephropathy is straightforward; it is defined by the presence of IgA-dominant or co-dominant immune deposits within glomeruli, as shown by immunohistochemistry or immunofluorescence. However, biopsies meeting this criterion may show a wide range of histological changes that reflect the clinical diversity of IgA nephropathy. Biopsy appearances may range from virtually normal histology by light microscopy to severe necrotizing, crescentic glomerulonephritis or advanced glomerulosclerosis, and tubular atrophy. There have been numerous clinicopathological studies of IgA nephropathy, the great majority being retrospective, correlating histological changes in diagnostic biopsy with clinical outcome. A number of histological lesions have been reported to be of prognostic value (Table 1).[1–15] The apparently conflicting results of these studies reflect differences in patient cohort, treatment, and clinical outcome measures. In general, studies in which the clinical end point is time to dialysis/renal failure have shown that chronic lesions (tubular atrophy, interstitial fibrosis, and glomerulosclerosis) are the most powerful histological predictors of outcome. This is not surprising, as these lesions reflect an advanced stage of disease; those patients who are biopsied and diagnosed late in the course of their disease will

**Table 1 | Histological risk factors for progressive renal failure in IgA nephropathy**

| Reference | Mesangial cellularity | Endocapillary proliferation | Crescents | Capillary wall IgA | Focal segmental sclerosis | Glomerulosclerosis | Interstitial fibrosis/tubular atrophy |
|---|---|---|---|---|---|---|---|
| Nozawa *et al.*[1] | | | | | | | X |
| Ballardie *et al.*[2] | X | | | | | | |
| To *et al.*[3] | | | | | | X | |
| Mera *et al.*[4] | | | | | | | X |
| Daniel *et al.*[5] | | | | | | | X |
| Vleming *et al.*[6] | | | | | | | X |
| Freese *et al.*[7] | | | X | X | | | X |
| Hogg *et al.*[8] | | | X | | | X | |
| Katafuchi *et al.*[9] | | | | | X | | X |
| Ibels *et al.*[10] | | | | | X | X | |
| Okada *et al.*[11] | | | | | | X | X |
| Bogenschutz *et al.*[12] | | | | | | | X |
| Rekola *et al.*[13] | X | | | | | | |
| D'Amico *et al.*[14] | | X | | X | | X | |
| Boyce *et al.*[15] | | | X | | | | |

X, statistically significant association with clinical outcome.

have a shorter time to end-stage renal disease. In contrast, those studies that have correlated histological changes with rate of loss of renal function or response to immunosuppressive therapy have shown that active glomerular lesions (mesangial, endocapillary or extracapillary proliferation, necrosis) are the most significant pathological prognostic factors.

There have been a number of attempts to incorporate the various histological lesions into a pathological classification of IgA nephropathy. None has achieved widespread acceptance. Deficiencies include a lack of definitions and use of vague terminology, lack of an evidence base, and inclusion of both active and chronic lesions in the definition of single categories. For example, a recent classification divides biopsies into four categories (I–IV), namely, no, slight (<10%), moderate (10–30%), and severe (>30%) glomerulosclerosis, crescent formation, or adhesion.[16] Although such a schema may accurately identify those patients who will develop renal failure, it cannot be used to guide patient management; clearly, the management of patients with class IV disease due to >30% glomerular crescents will differ from those with class IV disease due to diffuse glomerulosclerosis.

As described in the accompanying paper[17], we sought to develop an international consensus classification of IgA nephropathy with a strong evidence base. In this paper, we describe in detail the process by which histological data were collected and reviewed, and present the evidence used for selecting those pathological lesions that were included in the final schema (the 'Oxford Classification' of IgA Nephropathy). The overall philosophy was to collect a highly detailed initial pathological data set and to simplify this into a working schema. We recognize that a 'successful' classification must have clear definitions, be simple to use in routine clinical practice, be reproducible, and have a value independent of the clinical parameters at the time of biopsy. These criteria, therefore, formed the basis of our selection of which lesions to include in the final classification.

## RESULTS

### Pathology definitions

An initial meeting of pathologists was held in Oxford, UK, in 2005 to define the pathological variables to be assessed in renal biopsies in cases of IgA nephropathy. After a provisional analysis of the first 40 cases, areas of high interobserver variation were identified. To improve reproducibility, the definitions were refined at a meeting of pathologists in Atlanta, USA, in 2006 (Table 2). These were subsequently used for histological scoring of the entire study group. A minor amendment (in italics in Table 2) for defining necrosis in routine practice was agreed upon at a further meeting in Oxford in 2008.

### Scoring of histological lesions

A detailed pathology data set was collected initially, with the intention of working to simplify it for use in routine practice. Histology slides from each case were circulated among five pathologists in batches of five, in a rolling manner, to ensure that no two batches were scored by the same five pathologists. A score sheet was completed by individual pathologists for each biopsy (Table 3) using an agreed set of instructions (Table 4). Scoring of mesangial cellularity, together with other proliferative and sclerosing glomerular lesions, is illustrated in Figures 1 and 2. Completed score sheets were collected centrally by one of the pathologists (ISDR) and used to compile the extended pathological data set (Table 5). Completed score sheets were received from five pathologists for 47% of the cases, from four pathologists for 36% of the cases, and from three pathologists for 17% of the cases.

### Extended pathology data set

For most histological variables, the median score was taken for analysis (Table 5).

For scoring of glomerular crescents, the mean cellular and fibrocellular crescent scores were obtained by weighing the

**Table 2 | Pathological definitions**

*IgA nephropathy*: IgA nephropathy in the native kidney is defined as dominant or codominant staining with IgA in glomeruli by immunofluorescence or immunoperoxidase. Not all glomeruli need show this positivity. SLE-related nephritis should be excluded. The intensity of IgA staining should be more than trace. The distribution of IgA staining should include presence in the mesangium, with or without capillary loop staining, excluding a pure membranous, diffuse, global granular GBM staining pattern or a linear GBM staining pattern. IgG and IgM may be present, but not in greater intensity than IgA, except that IgM may be prominent in sclerotic areas. Complement 3 (C3) may be present. The presence of C1q staining in more than trace intensity should bring up consideration of lupus nephritis.

*Glomerular definitions*

*Diffuse*: A lesion involving most (⩾50%) glomeruli

*Focal*: A lesion involving <50% of glomeruli

*Global*: A lesion involving more than half of the glomerular tuft (See below for definitions of segmental and global sclerosis)

*Segmental*: A lesion involving less than half of the glomerular tuft (i.e., at least half of the glomerular tuft is spared). See below for definitions of segmental and global sclerosis

*Endocapillary hypercellularity*: Hypercellularity due to increased number of cells within glomerular capillary lumina, causing narrowing of the lumina

*Karyorrhexis*: Presence of apoptotic, pyknotic, and fragmented nuclei

*Necrosis* is defined by (i) disruption of the glomerular basement membrane with (ii) fibrin exudation and (iii) karyorrhexis. At least two of these three lesions need to be present to meet the criteria for necrosis. (*2008 Amendment: Necrosis should not be scored on the PAS-stained section alone; fibrin is more easily identified on H&E or MSB-stained sections, and breaks in the glomerular basement membrane are more easily identified on silver-stained sections. A minimum requirement for the definition of a necrotizing lesion is extracapillary fibrin exudation.*)

*GBM duplication*: A double contour of the GBM with or without endocapillary hypercellularity

*Increased mesangial matrix*: An increase in the extracellular material in the mesangium such that the width of the interspace exceeds two mesangial cell nuclei in at least two glomerular lobules

*Sclerosis*: Obliteration of the capillary lumen by increased extracellular matrix, with or without hyalinosis or foam cells

*An adhesion*: An area of continuity between the glomerular tuft and Bowman's capsule separate from an extracapillary lesion or from an area of segmental sclerosis

*Segmental sclerosis*: Any amount of the tuft involved with sclerosis, but not involving the whole tuft

*Global sclerosis*: The entire glomerular tuft involved with sclerosis

*Collapsed/ischemic glomerulus*: A glomerulus showing collapse of the capillary tuft with or without thickening of Bowman's capsule and fibrosis in the Bowman's space

*Extracapillary lesions* are subclassified as follows:

*Extracapillary proliferation or cellular crescent*: Extracapillary cell proliferation of more than two cell layers with >50% of the lesion occupied by cells. It is further classified by the percentage of glomerular circumference involved: <10, 10–25, 26–50, and >50%

*Extracapillary fibrocellular proliferation or fibrocellular crescent*: An extracapillary lesion comprising cells and extracellular matrix, with <50% cells and <90% matrix. This is further classified by the percentage of the glomerular circumference involved: <10, 10–25, 26–50, and >50%

*Extracapillary fibrosis or fibrous crescent*: >10% of the circumference of Bowman's capsule covered by a lesion composed of ⩾90% matrix. It is further classified by the percentage of the glomerular circumference involved: 10–25%, 26–50%, and >50%. Ischemic, obsolescent glomeruli should be excluded A crescent is one of these extracapillary lesions that involves >10% of the circumference of Bowman's capsule

*Mesangial hypercellularity* is subclassified as follows:

If <4 mesangial cells/mesangial area=normal,

4–5 mesangial cells/mesangial area=mild mesangial hypercellularity,

6–7 mesangial cells/mesangial area=moderate mesangial hypercellularity, and

8 or more mesangial cells/mesangial area=severe mesangial hypercellularity.

*Note*: This is scored for each glomerulus by assessing the most cellular mesangial area. Mesangial areas immediately adjacent to the vascular stalk should not be scored. Individual mesangial areas showing hypercellularity are separated by areas narrowing to the width of <2 mesangial cell nuclei (i.e., count clusters, not files of mesangial cell nuclei)

*Tubulointerstitial definitions*

*Tubular atrophy* is defined by thick irregular tubular basement membranes with decreased diameter of tubules. It is scored according to the percentage of cortical area involvement, with 1–5% rounded to 5% and other values rounded to the closest 10%

*Interstitial fibrosis* is defined as increased extracellular matrix separating tubules in the cortical area. It is scored as percentage involvement, with 1–5% rounded to 5% and other values rounded to the closest 10%.

*Interstitial inflammation* is defined as inflammatory cells within the *cortical* interstitium in excess. It is scored as percentage involvement, with 1–5% rounded to 5% and other values rounded to the closest 10%. It should be noted whether the inflammation is confined to the areas of interstitial fibrosis or not

*Additional tubular lesions* are noted as follows: The presence of numerous red blood cells, defined as tubules completely filled with red blood cells with or without casts, is noted as a lesion when it involves ⩾20% of tubules

*Acute tubular injury* of the proximal tubular epithelium is defined by simplification of the epithelium without tubular basement membrane thickening

*Vascular definitions*

*Arterial lesions* are scored based on the most severe lesions. Interlobular and larger arteries are scored separately. An interlobular artery is one surrounded by the cortex; an arcuate artery is one at the corticomedullary junction. Intimal thickening is scored by comparing the thickness of the intima to that of the media in the same segment of vessel. Score the intima variously as normal, and thickened to more or less than the thickness of the media.

*Arteriolar hyaline* is noted as the proportion of arterioles affected (0, 1–25%, 26–50%, >50%).

GBM, glomerular basement membrane; H&E, hematoxylin and eosin stain; MSB, Martius scarlet blue; PAS, periodic acid Schiff; SLE, systemic lupus erythematosus.

**Table 3 | Score sheet used for collecting detailed histological data set**

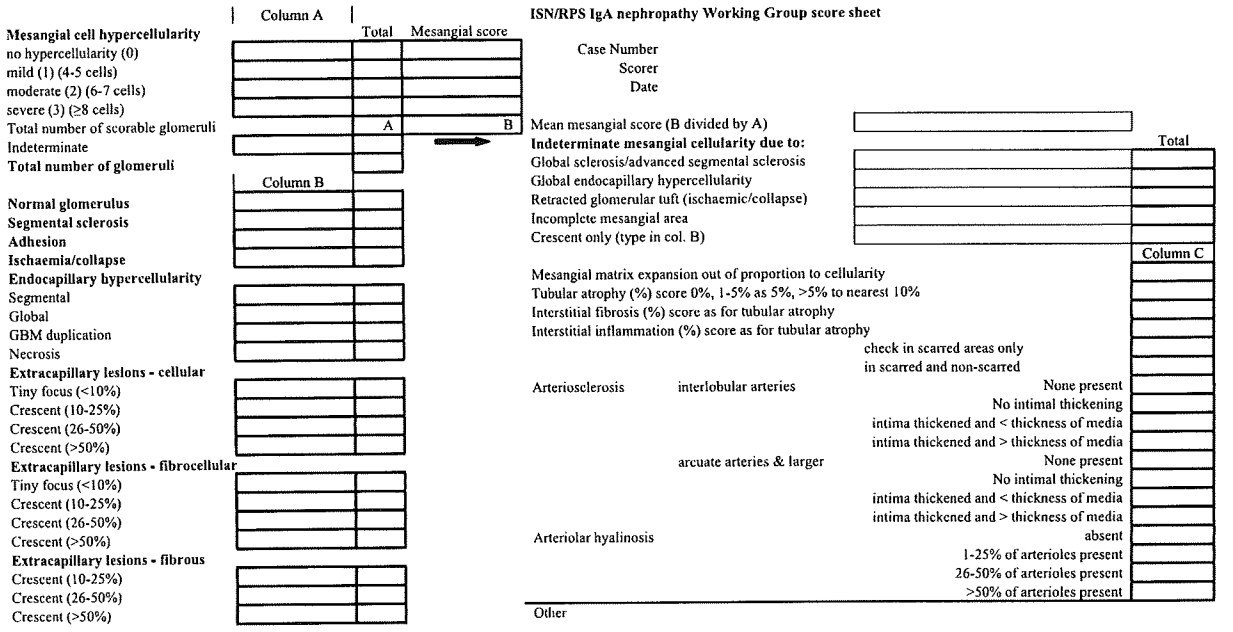


**Table 4 | Guidelines for completion of the light microscopy score sheet**

1. Using the circled PAS-stained section: for every glomerulus, mark one box only in Column A. If the indeterminate for mesangial cellularity box is marked, then mark which of the five reasons for not scoring mesangial cellularity applies. At least three mesangial cell areas should be present to score a glomerulus. In the global sclerosis category include both solidified and obsolescent glomeruli, and advanced segmental sclerosis when $<3$ mesangial areas remain. Mesangial cellularity is difficult to score in segments showing endocapillary hypercellularity. Therefore, glomeruli showing global endocapillary hypercellularity should be classed as indeterminate for mesangial cellularity (and the endocapillary lesions noted in column B). Score each glomerulus by assessing the most cellular mesangial area. Mesangial areas immediately adjacent to the vascular stalk should not be scored. Individual mesangial areas showing hypercellularity are separated by areas of narrowing to the width of $<2$ mesangial cell nuclei (i.e., count clusters, not files, of mesangial cell nuclei). Mesangial cell nuclei are those surrounded by the matrix; do not count those projecting into a capillary lumen
2. Using the circled PAS-stained section: for every glomerulus, mark none, one, or more than one box in Column B as appropriate
   A segmental lesion with capillary occlusion by both sclerosis and endocapillary hypercellularity should be scored for both. Endocapillary hypercellularity is defined by the presence of cells within capillary lumina, not by the matrix. Therefore, in the presence of segmental sclerosis, endocapillary hypercellularity can only be scored within that segment if preserved capillary loops are also present
   GBM duplication: score if it involves an open capillary loop but not as part of a sclerosed segment
3. Using any of the provided sections: for the whole biopsy, mark any box in Column C that applies
   When noting excessive mesangial matrix increase, assess only mesangial areas away from segmental sclerosis, i.e., associated with patent capillary loops
   For scoring arteriolar hyalinosis in Column C, examine only the PAS-stained section used for glomerular scoring
4. In the 'Other' box: note any other abnormality seen, e.g., a glomerular lesion present in one of the sections but not represented in the PAS section used for scoring, mesangiolysis, large numbers of RBC casts, ATN, and malignant vascular disease. Sections should be 2–3 μm thick for scoring. Note if the section appears thicker
5. Total number of glomeruli=total scorable glomeruli+total indeterminate for mesangial cellularity. To produce the mesangial score, multiply the totals of the boxes in column A by 0, 1, 2, or 3 as appropriate. The mean mesangial score is the total of the mesangial scores divided by the number of scorable glomeruli

ATN, acute tubular necrosis; GBM, glomerular basement membrane; PAS, periodic acid Schiff; RBC, red blood cell.

extracapillary lesions by size. A multiplication factor of 1 was applied for lesions $<10\%$ of the glomerular circumference, 2 for lesions 10–25% of the glomerular circumference, 3 for lesions 26–50% of the glomerular circumference, and 4 for lesions $>50\%$ of the glomerular circumference. The resulting scores were summed and divided by the total number of glomeruli in the biopsy.

Additional data items were derived from the completed score sheets to address specific questions. For example,

*Mesangial 1 versus 2*: Is the proportion of severely hypercellular glomeruli of different significance than that of the mean mesangial cellularity?

*Extracapillary 1 versus 2*: Are cellular and fibrocellular crescents of different significances?

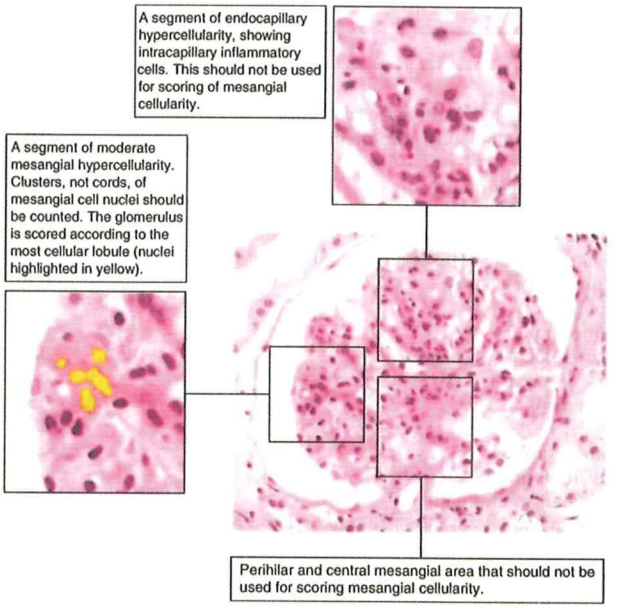


**Figure 1 | An illustration of mesangial cellularity scoring (objective ×40 original magnification, periodic acid Schiff stain).**

*Extracapillary 2 versus 3*: Is the size of a crescent significant?

*Interstitial inflammation 1 versus 2*: Is inflammation confined to areas of fibrosis of different significance compared with inflammation also involving non-fibrotic cortex?

*Arteriole 1 versus 2*: Is the extent of arteriolar hyalinosis, rather than merely its presence or absence, of significance?

The final, simplified set of pathological variables was selected on the basis of independence from other histological lesions, simplicity of assessment, and reproducibility.

### Reproducibility of pathology variables

During the development process, considerable effort was made to minimize interobserver variation between pathologists in the working group. It was agreed that histological lesions that continued to show poor reproducibility within this group should not be a part of the final classification, as the reproducibility is likely to be even lower among pathologists in routine clinical practice. Reproducibility was assessed statistically using intraclass correlation coefficients (ICCs), which are summarized in Table 5.

On the basis of the ICC scores, lesions were divided into three groups as follows:

*Group 1*: Those lesions showing good or very good reproducibility ($>0.6$) were mesangial cellularity score, percentage of global glomerulosclerosis, percentage of cellular + fibrocellular crescents, cellular + fibrocellular crescent score (including adjustment for size of crescent), tubular atrophy, interstitial fibrosis, interstitial inflammation 1, and arterial scores 1, 2, and 3.

*Group 2*: Those lesions showing moderate reproducibility (0.4–0.6) were extent of segmental glomerulosclerosis and percentage of glomeruli showing either segmental or global endocapillary hypercellularity.

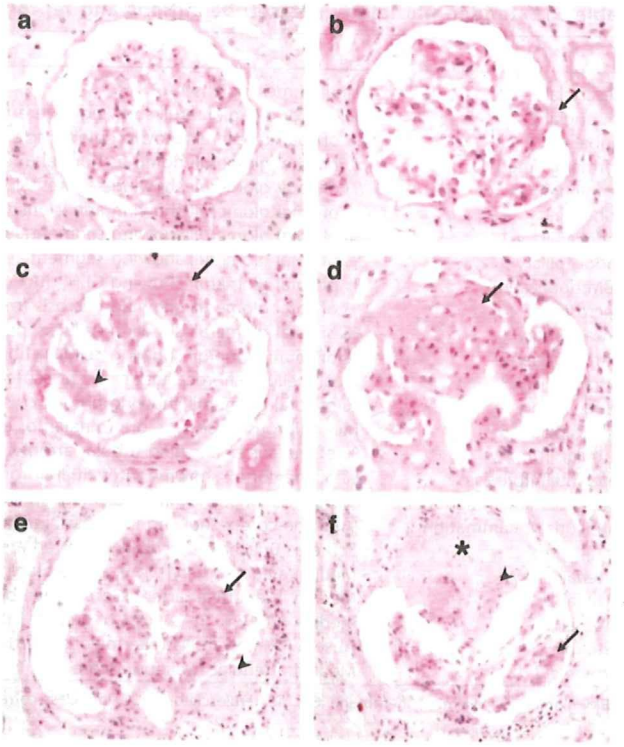


**Figure 2 | Proliferative and sclerosing glomerular lesions.** All figures objective ×40 original magnification, periodic acid Schiff stain. (**a**) Normal glomerulus by light microscopy. (**b**) Tuft adhesion (arrow) without segmental sclerosis. This lesion should be included with segmental sclerosis lesions for scoring purposes. (**c**) Segmental sclerosis (arrow) with a lobule away from the sclerosis showing moderate mesangial hypercellularity (arrowhead). (**d**) Extensive segmental sclerosis (arrow). This glomerulus should not be used for mesangial scoring. (**e**) A glomerulus showing severe mesangial hypercellularity (arrow) and a small cellular crescent (arrowhead; 10–25% of the glomerular circumference). (**f**) A glomerulus showing mild mesangial hypercellularity (arrow). There is segmental endocapillary hypercellularity (arrowhead); this segment should not be used for mesangial scoring. In addition, there is a cellular crescent (asterisk; 25–50% of the glomerular circumference).

*Group 3:* Those lesions showing poor or fair reproducibility ($<0.4$) were percentage of normal glomeruli, presence of adhesions, percentage of glomeruli showing segmental endocapillary hypercellularity, presence of glomerular basement membrane duplication, presence of necrosis, percentage of glomeruli showing fibrous crescents, interstitial inflammation 2 (inflammation involving non-fibrotic cortex), and arteriolar hyalinosis.

Those lesions in group 3 were excluded from the classification on the basis of poor reproducibility, with the exception of the following:

- *Adhesions*: Reproducibility increased when combined with segmental sclerosis, indicating that the low ICC score for adhesions alone resulted from different

**Table 5 | Extended pathology dataset: definitions and reproducibility**

| | | ICC |
|---|---|---|
| Mesangial 1 | Median mesangial score | 0.64 |
| Mesangial 2 | % of scorable glomeruli showing severe mesangial hypercellularity (median of group) | 0.54 |
| Global GS | % of total glomeruli showing global sclerosis or retracted glomerular tuft (median of group) | 0.90 |
| Normal glomeruli | % of total glomeruli noted as normal (median of group) | 0.27 |
| Segmental GS | % of total glomeruli showing segmental sclerosis (median of group) | 0.46 |
| Adhesion | % of total glomeruli showing adhesions (median of group) | 0.20 |
| Endocapillary 1 | % of total glomeruli showing segmental endocapillary hypercellularity (median of group) | 0.36 |
| Endocapillary 2 | % of total glomeruli showing segmental+global endocapillary hypercellularity (median of group) | 0.57 |
| GBM duplication | % of total glomeruli showing GBM duplication (median of group) | 0.10 |
| Necrosis | % of total glomeruli showing necrosis (median of group) | 0.31 |
| Extracapillary 1 | % of total glomeruli showing cellular crescents (median) | 0.62 |
| Extracapillary 2 | % of total glomeruli showing cellular+fibrocellular crescents (median) | 0.64 |
| Extracapillary 3 | Mean cellular+fibrocellular crescent score (median of group) | 0.66 |
| Extracapillary 4 | % of total glomeruli showing fibrous crescents (median) | 0.32 |
| Extracapillary 5 | Mean fibrous crescent score (median of group) | 0.34 |
| Tubular atrophy | % of the cortex showing tubular atrophy (median of group) | 0.79 |
| Interstitial fibrosis | % of the cortex showing interstitial fibrosis (median of group) | 0.78 |
| Interstitial inflammation 1 | % of the cortex showing interstitial inflammation (median of group) | 0.58 |
| Interstitial inflammation 2 | % of the cortex showing interstitial inflammation if majority (3 or more) checked scarred and non-scarred. Score as 0 if majority checked scarred areas only. Scarred only 0; scarred and non-scarred 1 | 0.03 |
| Arterial 1 | Median arcuate artery score. Leave blank if none present | 0.77 |
| Arterial 2 | Median interlobular artery score. Leave blank if none present | 0.69 |
| Arterial 3 | Median artery score—worst of arcuate and interlobular arteries. Leave blank if none present. | 0.69 |
| Arteriole 1 | Absent=0; present=1. Take majority verdict | 0.36 |
| Arteriole 2 | Median arteriolar hyalinosis score | 0.35 |

GBM, glomerular basement membrane; GS, glomerulosclerosis; ICC, intraclass correlation coefficient.

pathologists labeling the same lesion as either segmental sclerosis or an adhesion. For subsequent analysis, segmental sclerosis and adhesions were summed.

- *Necrosis*: At the Oxford 2008 meeting, periodic acid schiff (PAS)-stained sections and all other slides from cases in which at least one pathologist had recorded the presence of necrosis were reviewed independently by each of the pathologists. The initial scoring, on which the ICC is calculated, had been carried out on only a single circled PAS-stained section. Reproducibility was higher when all slides, rather than only the PAS-stained slide, were examined (data not shown). This review led to a further refinement of the definition of necrosis to increase reproducibility (see Table 2).
- *Endocapillary hypercellularity*: The ICC for the sum of percentage of segmental and global endocapillary hypercellularity was considerably higher than that for the percentage of segmental hypercellularity, indicating that there was poor reproducibility for the distinction of segmental from global lesions rather than for the identification of endocapillary hypercellularity. The sum of segmental and global endocapillary hypercellularity was, therefore, used in subsequent analyses.

### Correlation between pathology variables

Significant correlations between 23 pathology variables (excluding 'normal glomeruli') are shown in Table 6. Given the 253 different comparisons possible, the initial significance was set at $P=0.05/253$, that is, $P=0.0002$. Seventy-seven comparisons were considered statistically significant. Several of the strong correlations are not unexpected; for example, the correlations between interstitial fibrosis and tubular atrophy and between both of these and global glomerulosclerosis. However, there are other significant correlations that may be important in terms of pathogenesis. Thus, segmental sclerosis correlates with extracapillary lesions including either fibrocellular or fibrous crescents, suggesting a common pathogenesis. It is also of interest that capillary wall duplication, although poorly reproducible, does show a significant correlation with endocapillary proliferation.

Although many of the pathology variables showed a significant correlation with others, the correlation coefficient between some was so close to 1 that to include both in a classification would provide no additional value. For example, the '*R*' values for endocapillary 1 and 2 (0.99), extracapillary 2 and 3 (0.99), interstitial fibrosis and tubular atrophy (0.98), interstitial fibrosis and interstitial inflammation (0.9), interstitial fibrosis and global glomerulosclerosis (0.8), arterial 2 and 3 (0.9), and arteriole 1 and 2 (0.95) indicated that these pairs of variables were very closely linked.

The selection of which of the linked variables to include in the classification was based on reproducibility, ease of identification, and susceptibility to sampling error. For example, extracapillary 2, a simple calculation of % cellular + fibrocellular crescents, was preferred to extracapillary 3, a complex calculation requiring scoring of the size of the crescents in each glomerulus. Interstitial fibrosis and tubular atrophy were preferred to global glomerulosclerosis,

**Table 6 | Correlations between pathology variables**

| | Mesang | | GS | | | Endocap | | | | Extracap | | | | | Interstitium | | | | Vessels | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mes1 | Mes2 | GlobGS | SegGS | Adh | End1 | End2 | GBMdup | Necr | Extr1 | Extr2 | Extr3 | Extr4 | Extr5 | TubAt | IntFib | IntInfl1 | IntInfl2 | Art1 | Art2 | Art3 | Artiol1 | Artiol2 |
| Mes1 | — | 0.7 | | 0.2 | 0.3 | 0.3 | 0.3 | | | | 0.2 | 0.2 | | | | 0.2 | 0.3 | | | | | | |
| Mes2 | | — | | | 0.3 | 0.3 | 0.3 | | | | | | | | | | | | | | | | |
| GlobGS | | | — | 0.4 | 0.2 | | | | | | | | | | 0.7 | 0.8 | 0.6 | | | 0.3 | 0.3 | 0.4 | 0.3 |
| SegGS | | | | — | 0.5 | | | | | | 0.4 | 0.4 | 0.3 | 0.3 | 0.5 | 0.5 | 0.4 | | | | | | |
| Adh | | | | | — | | | | | | 0.3 | 0.3 | 0.2 | 0.2 | 0.3 | 0.3 | 0.3 | | | | | | |
| End1 | | | | | | — | 0.99 | 0.3 | | 0.4 | 0.5 | 0.5 | | | | | | | | | | | |
| End2 | | | | | | | — | 0.3 | | 0.4 | 0.5 | 0.5 | | | | | | | | | | | |
| GBMdup | | | | | | | | — | | | | | | | | | | | | | | | |
| Necr | | | | | | | | | — | | | | | | | | | | | | | | |
| Extr1 | | | | | | | | | | — | 0.7 | 0.7 | | | | | | | | | | | |
| Extr2 | | | | | | | | | | | — | 0.99 | 0.4 | 0.4 | | | | | | | | | |
| Extr3 | | | | | | | | | | | | — | 0.4 | 0.4 | | | 0.2 | | | | | | |
| Extr4 | | | | | | | | | | | | | — | 0.99 | | | | | | | | | |
| Extr5 | | | | | | | | | | | | | | — | | | | | | | | | |
| TubAt | | | | | | | | | | | | | | | — | 0.98 | 0.9 | | 0.8 | 0.3 | 0.3 | 0.4 | 0.4 |
| IntFib | | | | | | | | | | | | | | | | — | 0.9 | | 0.8 | 0.3 | 0.3 | 0.4 | 0.4 |
| IntInfl1 | | | | | | | | | | | | | | | | | — | | | | | 0.3 | |
| IntInfl2 | | | | | | | | | | | | | | | | | | — | | | | | |
| Art1 | | | | | | | | | | | | | | | | | | | — | 0.8 | 0.9 | 0.6 | |
| Art2 | | | | | | | | | | | | | | | | | | | | — | 0.9 | 0.5 | 0.5 |
| Art3 | | | | | | | | | | | | | | | | | | | | | — | 0.5 | 0.5 |
| Artiol1 | | | | | | | | | | | | | | | | | | | | | | — | 0.95 |
| Artiol2 | | | | | | | | | | | | | | | | | | | | | | | — |

Adh, adhesion; Art, arterial; Artiol, arteriole; End, endocapillary; Extr, extracapillary; GBMdup, glomerular basement membrane duplication; GlobGS, global glomerulosclerosis; IntFib, interstitial fibrosis; IntInfl, interstitial inflammation; Mes, mesangial; Necr, necrosis; SegGS, segmental glomerulosclerosis; TubAt, tubular atrophy.
Only statistically significant *R* values (correlation coefficients) are shown.
Statistically significant correlations were determined using the Holm-Bonferroni method to minimize the probability of making a Type I statistical error.

as their quantification is less susceptible to error owing to a paucity of glomeruli or because of subcapsular sampling.

### Mesangial hypercellularity score

On the basis of our selection criteria, mesangial hypercellularity score was included in the final schema. As reported in the accompanying paper, the optimal cutoff given by sensitivity analysis for predicting clinical outcome was 0.71, which was approximated to 0.5 for clinicopathological correlations, without a significant loss of sensitivity. Mesangial score was derived from scoring each individual glomerulus and taking the mean. Although it is reproducible, simple to perform, and of clinical significance, for some biopsies with large numbers of glomeruli, it can be time consuming. We therefore reasoned that not all pathologists would be willing or have time to score mesangial cellularity formally in routine practice. Therefore, a simpler alternative was tested, that is, dividing biopsies according to whether more or less than half of the glomeruli show mesangial hypercellularity. The relationship between this measure and the mesangial hypercellularity score was formally assessed at the final Oxford meeting. All pathologists were asked independently to provide a percentage of glomeruli showing mesangial hypercellularity for 16 cases from the study group that did not show endocapillary or extracapillary lesions (8 with mesangial score $>0.7$ and 8 with mesangial score $<0.7$). For all but one case with an original mesangial score of $<0.7$, the majority of pathologists scored the biopsies as $<50\%$ of glomeruli showing hypercellularity. For all cases with an original mesangial score of $>0.7$, the majority of pathologists scored the biopsies as $>50\%$ of glomeruli showing hypercellularity. For cases near the borderline, with an original mesangial score of 0.5–0.7, not surprisingly, there was high interobserver variation for the cutoff of 50% of glomeruli showing hypercellularity. On the basis of this evaluation, it was concluded that dividing biopsies according to whether more or less than 50% of glomeruli show mesangial hypercellularity is a suitable alternative to the formal mesangial hypercellularity score for use in everyday practice. However, for research studies and clinical trials, formal mesangial hypercellularity scores are recommended.

### Pathology variables assessed in the final classification

As described above, the initial pathology variables were refined by excluding those with poor interobserver reproducibility and only including one variable from those pairs or groups that were shown to be strongly correlated. This left the following variables, all common in IgA nephropathy, to be further analyzed in relation to the clinical data:

(1) mesangial cellularity score;
(2) percentage of glomeruli showing segmental adhesions or sclerosis;
(3) percentage of glomeruli showing endocapillary hypercellularity;
(4) percentage of glomeruli showing cellular or fibrocellular crescents;
(5) percentage of interstitial fibrosis/tubular atrophy; and
(6) arterial score

The accompanying paper describes the further analysis of these variables in relation to clinical presentation and outcome.

### Adequacy of biopsies for classification

The minimum number of glomeruli for a biopsy to be included in the study was initially set at eight. The median number of glomeruli in the 265 biopsies meeting inclusion

criteria was 18. To determine whether the number of glomeruli in a biopsy influences the histological scores, the glomerular number was correlated with scores for the 25 histological lesions. There was no significant correlation, other than with endocapillary and extracapillary proliferation. These showed a weak positive correlation with the number of glomeruli in a biopsy. For endocapillary 2 versus number of glomeruli, Spearman's correlation coefficient was 0.22 ($P \leqslant 0.001$), and for extracapillary 2 versus number of glomeruli, Spearman's correlation coefficient was 0.15 ($P = 0.014$).

To better illustrate these findings, the biopsies were then divided into three groups according to the number of glomeruli: 8–12 ($n = 69$), 13–17 ($n = 59$), and $\geqslant 18$ glomeruli ($n = 137$). Scores for the 25 histological lesions were compared between these groups. There was no significant difference in the mean score for any lesion between the biopsies with 8–12 and 13–17 glomeruli. Biopsies with $\geqslant 18$ glomeruli showed marginally but statistically significant higher mean scores for only three lesions: mesangial 2 ($8.1 \pm 13.4$ versus $5.7 \pm 13.2$ for 8–12 glomeruli, and $6.0 \pm 13.4$ for 13–17 glomeruli, $P = 0.01$), endocapillary 1 ($6.3 \pm 8.9$ versus $5.3 \pm 11.8$ for 8–12 glomeruli, and $5.3 \pm 10.3$ for 13–17 glomeruli, $P = 0.01$), and endocapillary 2 ($7.9 \pm 13.1$ versus $6.5 \pm 5.1$ for 8–12 glomeruli and $5.9 \pm 12.2$ for 13–17 glomeruli, $P = 0.006$).

## DISCUSSION

Our aim was to design a systematic approach for the development of a reproducible pathological classification of IgA nephropathy that would predict clinical outcome. To this end, we collected cases with defined clinical outcomes and assessed a range of features in the renal biopsies. We proceeded by first assessing the reproducibility of the scoring of individual biopsy features, then asking which features showed good reproducibility and were independent, and finally asking which of those were related to presenting clinical parameters and had an independent relevance to clinical outcome. Although this seems to be a logical way to develop a classification, this approach has not generally been followed in renal pathology. Thus, the classification schemes for lupus nephritis, as first defined in the World Health Organization (WHO) classifications and subsequently in the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification,[18] were developed by groups of experts without any attempt to show that the definitions or the classes were reproducible entities. Subsequent testing has shown areas of high interobserver variation, with $\kappa$-scores $< 0.4$ for differentiating active from chronic and segmental from global in class IV disease.[19] In addition, the classifications were not tested for their predictive value before publication, although this has been done subsequently.[20,21] With regard to earlier classification schemes in IgA nephropathy, several of these have been tested for their predictive value, but, in many cases, the variables used in the classifications were not systematically defined, and in no case was there an attempt to examine the reproducibility of the histological variables that were assessed. For example, in the Lee classification,[22] the vague terminology used (terms such as mostly, occasional, frequent, and localized) makes the schema difficult to be employed in a reproducible way. Consequently, earlier histological classifications of IgA nephropathy have not been accepted by the majority of nephropathologists. In a 2006 Renal Pathology Society survey, only 37% of responding pathologists used a classification system for reporting IgA nephropathy biopsies. Five different schema were used, of which that of Haas[23] was the most popular, but even this was used by only 14% of pathologists (38% of those who used a classification system).

The range of histological features we studied was restricted to those that can be assessed by light microscopy, and all the included features had been suggested by earlier studies to have an effect on outcome. Our initial definitions followed those used earlier in the WHO atlas of glomerular diseases[24] and in the classification of lupus nephritis.[18] Although the definitions seemed straightforward and well established, it is important to recognize that some have not been easy to apply in practice. Perhaps the most critical of these was the definition of mesangial hypercellularity, which is a typical feature in IgA nephropathy. Our scoring system depended on assessing the number of nuclei in glomerular mesangial areas, but it became clear at the second meeting of pathologists that there was uncertainty about what constituted a mesangial area; hence, a revision of the definition was necessary. A problem was also encountered with the definition of necrosis, which needed to be revised as shown in Table 2. Cellular crescents are most commonly defined as extracapillary proliferation involving at least 25% of the glomerular circumference. We also noted smaller foci of extracapillary proliferation (10–25 and $< 10\%$ of the glomerular circumference) in our biopsies, and sought to determine whether the size, rather than merely the extent, of crescents was of independent significance. The correlation between the percentage of glomeruli with crescents and the crescent score (that included a multiplier for size of the individual crescentic lesions) was very close indeed, $r = 0.99$, indicating that subdividing crescents by size provided no additional information.

For each of the variables scored, we assessed the ICC. It is notable that some features in which the definitions seemed simple were poorly reproducible, for example, glomerular basement membrane duplication, fibrous crescents, and arteriolar hyaline. We have not further examined why there is such poor agreement on these features. One limitation of our study is that, in order to ensure consistency across pathologists, we restricted the scoring to a single PAS-stained section. Although we believe that most of the features examined would be seen well in PAS-stained sections, this might explain the variability of glomerular basement membrane duplication that is more reliably assessed in silver stains. We also found that necrosis could not be reliably

assessed on the PAS stain. It is also of note that reproducibility of the percentage of 'normal' glomeruli was poor. This may not be surprising when one considers the nature of IgA nephropathy. Unlike pauci-immune vasculitic glomerulonephritis, in which lesions are truly focal and segmental, all glomeruli in IgA nephropathy are abnormal to some extent, in that all contain mesangial IgA deposits. The most minor changes are detectable only on immunostaining or on electron microscopy, but large deposits may be seen on PAS stain, even in the absence of proliferation, and a subtle increase in mesangial matrix frequently accompanies the deposits. It is likely that the difference between pathologists in identifying these very mild changes at light microscopy explains the poor ICC for 'normal' glomeruli.

It could be argued that the good interobserver reproducibility we have achieved for some variables reflects the fact that the scoring was carried out by a group of pathologists who had met together on several occasions and that such good reproducibility may not translate into clinical pathology practice. Although this may be true, we feel that it is important that we have shown that the features retained in the classification had good reproducibility and, when several different features were strongly correlated, we used the one feature easiest to identify and least susceptible to sampling error.

An important question for many renal diseases is the issue of how much tissue is required for reliable diagnosis and classification. The answer depends, to a certain extent, on the nature of the condition. In general, diffuse glomerular diseases will require fewer glomeruli than those in which the pathology is focal. In the case of IgA nephropathy, glomerular IgA deposits are diffuse and a biopsy containing a single glomerulus may be sufficient to make a firm diagnosis. Many of the glomerular lesions, however, are focal, including endocapillary and extracapillary proliferation and segmental sclerosis. Thus, to apply a classification that includes quantitation of these lesions will require more than one glomerulus. We initially set the minimum number of glomeruli for inclusion in the study at eight. This limit was chosen, as it had been used in earlier studies of IgA nephropathy[2] and was similar to the criterion used in other conditions, such as the Banff classification of allograft pathology (8 glomeruli) and the ISN/RPS classification of lupus nephritis (10 glomeruli). We subsequently analyzed the histological scores according to biopsy size, in order to test the validity of using eight glomeruli as a criterion for adequacy. It is not surprising that some of the focal lesions (endocapillary and extracapillary proliferation scores) showed a weak correlation with the number of glomeruli. This is unlikely to be clinically relevant; those biopsies with the fewest glomeruli (8–12) showed no difference in mean scores compared with those with 13–17 glomeruli. Although those biopsies containing numbers of glomeruli above the median for the whole group (18) had significantly more severe mesangial and endocapillary lesions than those below the median, it would be impractical to exclude 50% of biopsies from classification on the basis of a minor difference in some focal lesions.

The statistical methodology used to develop this classification merits clarification. We used the ICC to address the reliability of multiple raters. This flexible method is an extension of the commonly used κ-statistic that is used to assess the agreement between two diagnostic tests, but applied to $>2$ raters and/or ordinal or continuous measurements.[25] Perfect agreement is indicated by an ICC of 1, and pure chance is indicated by a score of 0. The interpretation of the coefficient levels can be subjective, but authors have suggested a minimum of 0.4 as being necessary to define fair agreement.[26,27]

Given the number of variables studied and the exploratory nature of the work, numerous statistical tests were carried out, but appropriate precautions were taken to minimize type 1 error, that is, falsely rejecting the null hypothesis and assuming statistically significant differences between two variables. This was addressed using the Holm–Bonferroni method for multiple comparisons,[28,29] a valid modification of the more stringent Bonferroni correction.[30]

In summary, we have described here a systematic approach to developing a histological scoring scheme in IgA nephropathy. The results that we have found for interobserver reproducibility for individual features are likely to be applicable to other types of glomerulonephritis, but it should not be assumed that this will be true for the correlations between variables that may depend on the underlying pathobiology of each glomerular disease. We believe that our approach can act as a model for developing classifications for other types of renal disease. The accompanying paper describes the way in which the histological features described here relate to clinical outcome.

## MATERIALS AND METHODS

The overall design of the study, patient cohort, clinical data set, and clinicopathological correlations are described in the accompanying paper. Briefly, clinical data and renal biopsy material from 265 patients with IgA nephropathy were collected from 8 countries from 4 continents. Five centers from Asia, six from Europe, two from the United States, one from South America, and two multicenter networks (Canada and the United States) participated.

Biopsies containing $<8$ glomeruli were regarded as inadequate for scoring and were excluded from the analysis.

### Statistical methods

We assessed reproducibility for each variable of the extended pathology data set using ICC.[31] The ICC is a measure of reproducibility applicable to multiple raters. By convention, ICC of $<0.40$ is poor inter-rater reliability, 0.40–0.59 is moderate, 0.60–0.79 is substantial, and 0.80 is outstanding.[32,33]

Correlations between pathology variables were carried out using the Pearson test or the Spearman test appropriately. Given the number of possible comparisons between pathology variables, we used the Holm–Bonferroni method to minimize the risk of making a type 1 statistical error.[28,29] Briefly, this methodology compares the smallest $P$-value of all ($k$) comparisons with an $\alpha$-value of $0.05/k$. If that $P$-value is $<0.05/k$, the association is considered to be

statistically significant (reject the null hypothesis). The next smallest *P*-value is then compared with $0.05/(k-1)$, the following with $0.05/(k-2)$, etc. This continues until a *P*-value is superior to the calculated α-value, at which point, the procedure is stopped and all remaining comparisons are considered not statistically different (accept all other null hypotheses).

Analyses were carried out using SPSS software (version 11, SPSS. Chicago IL, USA).

## DISCLOSURE

All the authors declared no competing interests.

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## REFERENCES

1. Nozawa R, Suzuki J, Takahashi A *et al.* Clinicopathological features and the prognosis of IgA nephropathy in Japanese children on long-term observation. *Clin Nephrol* 2005; **64**: 171–179.
2. Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J Am Soc Nephrol* 2002; **13**: 142–148.
3. To KF, Choi PC, Szeto CC *et al.* Outcome of IgA nephropathy in adults graded by chronic histological lesions. *Am J Kidney Dis* 2000; **35**: 392–400.
4. Mera J, Uchida S, Nagase M. Clinicopathologic study on prognostic markers in IgA nephropathy. *Nephron* 2000; **84**: 148–157.
5. Daniel L, Saingra Y, Giorgi R *et al.* Tubular lesions determine prognosis of IgA nephropathy. *Am J Kidney Dis* 2000; **35**: 13–20.
6. Vleming LJ, de Fijter JW, Westendorp RG *et al.* Histomorphometric correlates of renal failure in IgA nephropathy. *Clin Nephrol* 1998; **49**: 337–344.
7. Freese P, Norden G, Nyberg G. Morphologic high-risk factors in IgA nephropathy. *Nephron* 1998; **79**: 420–425.
8. Hogg RJ, Silva FG, Wyatt RJ *et al.* Prognostic indicators in children with IgA nephropathy—report of the Southwest Pediatric Nephrology Study Group. *Pediatr Nephrol* 1994; **8**: 15–20.
9. Katafuchi R, Oh Y, Hori K *et al.* An important role of glomerular segmental lesions on progression of IgA nephropathy: a multivariate analysis. *Clin Nephrol* 1994; **41**: 191–198.
10. Ibels LS, Gyory AZ. IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine (Baltimore)* 1994; **73**: 79–102.
11. Okada H, Suzuki H, Konishi K *et al.* Histological alterations in renal specimens as indicators of prognosis of IgA nephropathy. *Clin Nephrol* 1992; **37**: 235–238.
12. Bogenschutz O, Bohle A, Batz C *et al.* IgA nephritis: on the importance of morphological and clinical parameters in the long-term prognosis of 239 patients. *Am J Nephrol* 1990; **10**: 137–147.
13. Rekola S, Bergstrand A, Bucht H. IGA nephropathy: a retrospective evaluation of prognostic indices in 176 patients. *Scand J Urol Nephrol* 1989; **23**: 37–50.
14. D'Amico G, Minetti L, Ponticelli C *et al.* Prognostic indicators in idiopathic IgA mesangial nephropathy. *Q J Med* 1986; **59**: 363–378.
15. Boyce NW, Holdsworth SR, Thomson NM *et al.* Clinicopathological associations in mesangial IgA nephropathy. *Am J Nephrol* 1986; **6**: 246–252.
16. Wakai K, Kawamura T, Endoh M *et al.* A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. *Nephrol Dial Transplant* 2006; **21**: 2800–2808.
17. Cattran D, Coppo R, Cook T *et al.* The Oxford Classification of IgA nephropathy: Rationale, clinicopathological correlations and classification. *Kidney Int* 2009; in press.
18. Weening JJ, D'Agati VD, Schwartz MM *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; **15**: 241–250.
19. Furness PN, Taub N. Interobserver reproducibility and application of the ISN/RPS classification of lupus nephritis—a UK-wide study. *Am J Surg Pathol* 2006; **30**: 1030–1035.
20. Yokoyama H, Wada T, Hara A *et al.* The outcome and a new ISN/RPS 2003 classification of lupus nephritis in Japanese. *Kidney Int* 2004; **66**: 2382–2388.

21. Hill GS, Delahousse M, Nochy D *et al.* Class IV-S versus class IV-G lupus nephritis: clinical and morphologic differences suggesting different pathogenesis. *Kidney Int* 2005; **68**: 2288–2297.
22. Lee SMK, Rao VM, Franklin WA *et al.* IgA nephropathy: morphologic predictors of progressive renal disease. *Hum Pathol* 1982; **13**: 314–322.
23. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. *Am J Kid Dis* 1997; **29**: 829–842.
24. Churg J, Bernstein J, Glassock RJ. *Renal Disease: Classification and Atlas of Glomerular Diseases*. Igaku-Shoin: New York, 1995.
25. Hripcsak G, Heitjan DF. Measuring agreement in medical informatics reliability studies. *J Biomed Inform* 2002; **35**: 99–110.
26. Fleiss JL. *Statistical Methods for Rates and Proportions*. John Wiley: New York, 1981, pp 212–236.
27. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics* 1977; **33**: 363–374.
28. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979; **6**: 65–70.
29. Norman G, Streiner D. *Biostatistics, The Bare Essentials*. Hamilton, Ontario: BC Decker Inc, 2000.
30. Aickin M, Gensler H. Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. *Am J Public Health* 1996; **86**: 726–728.
31. Armstrong GD. The intraclass correlation as a measure of interrater reliability of subjective judgments. *Nurs Res* 1981; **30**: 314–315, 320A.
32. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159–174.
33. Koch GG, Landis JR, Freeman JL *et al.* A general methodology for the analysis of experiments with repeated measurement of categorical data. *Biometrics* 1977; **33**: 133–158.

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ORIGINAL ARTICLE

# A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity

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**Abstract**
*Background* The etiology, prevalence, and prognosis of rapidly progressive glomerulonephritis (RPGN) including renal vasculitis vary among races and periods.
*Method* To improve the prognosis of Japanese RPGN patients, we conducted a nationwide survey of RPGN in the nephrology departments of 351 tertiary hospitals, and found 1772 patients with RPGN (Group A: diagnosed between 1989 and 1998, 884 cases; Group B: diagnosed between 1999 and 2001, 321 cases; and Group C: diagnosed between 2002 and 2007, 567 cases). ANCA subclasses, renal biopsy findings, treatment, outcome and cause of death were recorded.
*Result* The most frequent primary disease was renal-limited vasculitis (RLV) (42.1%); the second was microscopic polyangiitis (MPA) (19.4%); the third was anti-GBM-associated RPGN (6.1%). MPO-ANCA was positive in 88.1% of RLV patients and 91.8% of MPA patients. The proportion of primary renal diseases of RPGN was constant during those periods. The most frequent cause of death was infectious complications. The serum creatinine at presentation and the initial dose of oral

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prednisolone decreased significantly in Groups B and C compared to Group A. However, both patient and renal survival rates improved significantly in Groups B and C (survival rate after six months in Group A: 79.2%, Group B: 80.1%, and Group C: 86.1%. Six-month renal survival in Group A: 73.3%, Group B: 81.3%, and Group C: 81.8%).

*Conclusion* Early diagnosis was the most important factor for improving the prognosis of RPGN patients. To avoid early death due to opportunistic infection in older patients, a milder immunosuppressive treatment such as an initial oral prednisolone dose reduction with or without immunosuppressant is recommended.

**Keywords** Anti-neutrophil cytoplasmic antibody (ANCA) · Myeloperoxidase (MPO) · Microscopic polyangiitis (MPA) · Renal vasculitis · Rapidly progressive glomerulonephritis (RPGN) · RPGN clinical grading system

## Introduction

Rapidly progressive glomerulonephritis (RPGN) is defined as a clinical syndrome involving abrupt or insidious onset of hematuria, proteinuria, anemia, and rapidly progressive renal failure. The number of RPGN patients has increased recently [1], which may be a consequence of the wider availability of anti-neutrophil cytoplasmic autoantibody (ANCA) assays, improved recognition of the disease, increased referral rates to tertiary centers, and more efficient approaches to renal biopsy in recent years [2]. Furthermore, the prognosis for patients with RPGN is regarded as having improved over the last 20 years [2], especially the short-term prognosis of renal-limited vasculitis [3]. In contrast, the prognosis for older patients with RPGN and the long-term renal survival of patients with RPGN are still a concern [4–6]. RPGN is a condition that is not commonly encountered in individual nephrology departments, and the etiology of RPGN is diverse. Consequently, we started this observational study in 1998 to clarify the actual status of Japanese patients with RPGN, treatment attitudes regarding RPGN, the prognosis for these patients, and to formulate clinical guidelines for Japanese patients with RPGN. To do this, we conducted a nationwide survey of RPGN patients between 1989 and 2007. In 2002, we published our Japanese clinical guidelines for RPGN based on the survey results for 715 cases of RPGN in Japan [7]. From our observational study, we showed yearly changes in both primary renal diseases for RPGN, and the effect of the clinical guidelines on both the physician's treatment attitude toward RPGN patients and the outcome before and after the clinical guidelines had been published. Furthermore, we evaluated the effect of the Japanese clinical guidelines for RPGN on the outcome by analyzing our prospective cohort of RPGN patients in Japan.

## Subjects and methods

### Subjects

We retrospectively collected records of patients with RPGN from 1989 to 1998 and prospectively collected the clinical records of RPGN patients from 1999 to 2007 by mailing a questionnaire form annually to 351 nephrology departments of tertiary hospitals in Japan. This study was approved by the medical ethics committee at the Graduate School of Comprehensive Human Sciences, University of Tsukuba in accordance with the guidelines on epidemiological research from the Ministry of Health, Labor and Welfare of Japan. The definition of RPGN was based on clinical findings as follows: rapidly progressing renal failure from several weeks to a few months accompanied by the following nephritic urinary abnormalities: hematuria (mostly microscopic hematuria, but occasionally gross hematuria), proteinuria, and red blood cell casts or granular casts in the urine sediment. One hundred seventy-one nephrology departments responded and presented 1772 RPGN cases for this study.

We evaluated the RPGN cases by stratifying patients into three periods depending on the year of diagnosis of RPGN. The RPGN patients who were diagnosed between 1989 and 1998 were classified into the first period (Group A: 884 cases), and these subjects were retrospective cases. The RPGN patients who were diagnosed between 1999 and 2001 were classified into the second period (Group B: 321 cases); this was the period when we started the analysis of Japanese cases of RPGN and when some of the results were announced in Japan. The RPGN patients who were diagnosed between 2002 and 2007 were classified into the third period (Group C: 567 cases); this was the period after we had published the Japanese guidelines for RPGN in 2002 [7].

### Clinical evaluation and treatment methods

Baseline characteristics including age, sex, comorbid conditions, features of prodromal illness, and clinical, biochemical, serological, and urinary features at patient presentation were obtained from clinical records. Follow-up clinical data including serum creatinine, ANCA titer, anti-GBM anitibody titer, C-reactive protein, recurrence and outcome concerning survival, dialysis dependence after 1, 2, 3, 6, 12, and 24 months, start of dialysis therapy, the final follow-up date, and cause of death were also documented. Relapse was defined as a rise in the creatinine

concentration with nephritic sediment and other signs or symptoms of vasculitis. The initial dose of oral prednisolone, its duration of initial dose, and immunosuppressive treatment were also recorded.

The classification of RPGN was based on Glassock's classification [8]. The diagnosis of primary renal disease for RPGN was made by each institution.

### Statistical analysis

Regarding differences in the continuous variables between the groups, the unpaired Student's *t* test was applied after a symmetrical distribution was confirmed. Otherwise, the Mann–Whitney *U* test was applied. We used the chi-square test to analyze the frequencies of categorical variables. Both renal and patient survival rates were estimated by the Kaplan–Meier method. A prognostic factor was determined by the chi-square test, and then hazard ratios for patient outcome were estimated using a Cox regression model after confirming the proportionality in each model. To evaluate prognostic factors among our subjects at the start of treatment, we selected age, renal function (serum creatinine, urinary volume), glomerular damage (hematuria, proteinuria, cast formation), general status (serum albumin, serum total protein, hemoglobin), systemic inflammation (C-reactive protein, erythrocyte sedimentation rate, WBC count), and extrarenal complications (blood pressure, presence of lung involvement). Lung involvement indicates existence of chest X-ray abnormality, interstitial pneumonitis or lung bleeding. A $p$ value of less than 0.05 was considered significant. The statistical analyses were performed in part using SPSS software v.15.0.

## Results

### Classification, causes, and yearly changes of RPGN in Japan

Table 1 shows the number of patients with RPGN and yearly changes in frequencies. Among the total RPGN patients, 42.0% showed pauci-immune-type crescentic GN (renal-limited vasculitis: RLV), 19.4% MPA, and 2.6% Wegener's granulomatosis; thus, 64.0% exhibited pauci-immune-type RPGN. Anti-GBM-type RPGN and Goodpasture's syndrome were exhibited by 6.1% of RPGN patients. Among cases of primary crescentic GN, only 2.0% were immune-complex-type RPGN. Most of the cases of immune-complex-type RPGN were secondary RPGN due to other primary glomerulonephritis or secondary RPGN due to lupus or cryoglobulinemia.

Among patients with pauci-immune-type RPGN, the proportion of RLV was slightly decreased, whereas the proportion of MPA was increased during the observation period. The rate of patients with anti-GBM antibody was constant, and one quarter of these had been complicated with lung disease during the last 20 years (namely Goodpasture's Syndrome). The number and proportion of primary immune-complex-type RPGN cases among the total decreased recently.

Among all RPGN patients, female subjects were predominant. This difference was mainly due to patients with systemic lupus erythomatosus (SLE) and MPA. On the other hand, a slight male predominance was observed in patients with Wegener's granulomatosis. Among all RPGN subjects, the mean age significantly increased during the observation period. The main reason for this change was a significant increase in the mean age of subjects with RLV, MPA, and anti-GBM antibody-mediated RPGN in recent years (Table 2).

### Yearly changes in renal function and other values at presentation during the observation period

The mean serum creatinine level at presentation among all RPGN patients was significantly reduced in Groups B and C compared to Group A. However, serum creatinine at presentation was not reduced in anti-GBM antibody-associated crescentic GN, Goodpasture's syndrome, SLE, and Wegener's granulomatosis. Urinary protein at presentation was significantly reduced in anti-GBM antibody-associated crescentic GN between Groups B and C, and in SLE between Groups A and C. However, urinary protein was significantly increased in immune-complex-associated GN between Groups A and C, and in RLV between Groups A and B. CRP was significantly increased in Goodpasture's syndrome between Groups A and B, and Groups A and C, and significantly decreased in MPA between Groups A and C. There was no significant difference in hemoglobin at presentation during the observation period (Table 3). Among all RPGN patients, 18.8% of the subjects had interstitial pneumonitis, and 10.5% of the subjects had lung bleeding.

The prevalence of ANCA subgroups was analyzed in the subjects with RLV, MPA, and Wegener's granulomatosis (Table 4). The positive rate of MPO-ANCA among patients with RLV was 88.1%, that of MPA was 91.8%, and that of Wegener's granulomatosis was 22.7%. The positive rate of PR3-ANCA among patients with RLV was 7.4%, that of MPA was 6.1%, and that of Wegener's granulomatosis was 71.1%. Furthermore, 38 patients with RLV, 13 patients with MPA and 3 patients with Wegener's granulomatosis were both MPO-ANCA and PR3-ANCA positive, and 71 patients with RLV, 21 patients with MPA and 6 patients with Wegener's granulomatosis were both MPO-ANCA and PR3-ANCA negative.

**Table 1** Number of patients with RPGN and yearly changes in frequencies

| Diagnosis | Classification | Group A | | Group B | | Group C | Total RPGN cases | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % | *n* | % |
| Primary | | | | | | | | | |
| Crescentic GN | Anti-GBM antibody-associated crescentic GN | 39 | 4.4 | 20 | 6.2 | 22 | 3.9 | 81 | 4.6 |
| | Immune-complex-associated crescentic GN | 26 | 2.9 | 3 | 0.9 | 6 | 1.1 | 35 | 2.0 |
| | Renal-limited vasculitis | 345 | 39.0 | 151 | 47.0 | 249 | 43.9 | 745 | 42.0 |
| | Overlapped crescentic GN | 19 | 2.1 | 5 | 1.6 | 7 | 1.2 | 31 | 1.7 |
| | Undifferentiated primary crescentic GN | 14 | 1.6 | 2 | 0.6 | 12 | 2.1 | 28 | 1.6 |
| Primary GN with crescents | Mesangioproliferative glomerulonephritis | 9 | 1.0 | 2 | 0.6 | 4 | 0.7 | 15 | 0.8 |
| | Membranous nephropathy | 2 | 0.2 | 2 | 0.6 | 1 | 0.2 | 5 | 0.3 |
| | IgA nephropathy | 25 | 2.8 | 9 | 2.8 | 9 | 1.6 | 43 | 2.4 |
| | Non-IgA mesangial proliferative GN | 4 | 0.5 | 2 | 0.6 | 2 | 0.4 | 8 | 0.5 |
| | Other primary GN | 2 | 0.2 | 0 | 0.0 | 1 | 0.2 | 3 | 0.2 |
| Systemic disease-associated | | | | | | | | | |
| | Goodpasture's syndrome | 14 | 1.6 | 5 | 1.6 | 8 | 1.4 | 27 | 1.5 |
| | Systemic lupus erythematosus | 50 | 5.7 | 5 | 1.6 | 11 | 1.9 | 66 | 3.7 |
| | Wegener's granulomatosis | 23 | 2.6 | 9 | 2.8 | 14 | 2.5 | 46 | 2.6 |
| | Microscopic polyangiitis | 157 | 17.8 | 58 | 18.1 | 129 | 22.8 | 344 | 19.4 |
| | Other necrotizing vasculitis | 6 | 0.7 | 5 | 1.6 | 4 | 0.7 | 15 | 0.8 |
| | Purpura nephritis | 18 | 2.0 | 5 | 1.6 | 13 | 2.3 | 36 | 2.0 |
| | Cryoglobulinemia | 5 | 0.6 | 3 | 0.9 | 4 | 0.7 | 12 | 0.7 |
| | Rheumatoid arthritis | 18 | 2.0 | 2 | 0.6 | 4 | 0.7 | 24 | 1.4 |
| | Malignant neoplasm | 2 | 0.2 | 1 | 0.3 | 0 | 0.0 | 3 | 0.2 |
| | Other systemic diseases | 22 | 2.5 | 9 | 2.8 | 9 | 1.6 | 40 | 2.3 |
| Infection-associated | | | | | | | | | |
| | Poststreptococcal acute glomerulonephritis | 8 | 0.9 | 2 | 0.6 | 0 | 0.0 | 10 | 0.6 |
| | Abscess | 1 | 0.1 | 2 | 0.6 | 3 | 0.5 | 6 | 0.3 |
| | Hepatitis C virus | 1 | 0.1 | 1 | 0.3 | 0 | 0.0 | 2 | 0.1 |
| | Other infectious diseases | 13 | 1.5 | 2 | 0.6 | 5 | 0.9 | 20 | 1.1 |
| Drug-associated | | 7 | 0.8 | 1 | 0.3 | 2 | 0.4 | 10 | 0.6 |
| Others | | 7 | 0.8 | 1 | 0.3 | 9 | 1.6 | 17 | 1.0 |
| Unknown | | 47 | 5.3 | 14 | 4.4 | 39 | 6.9 | 100 | 5.6 |
| Total | | 884 | 100.0 | 321 | 100.0 | 567 | 100.0 | 1772 | 100.0 |

## Prognosis and cause of death

During the entire observation period, 351 patients (39.7%) died in Group A, 110 patients (34.3%) died in Group B, and 102 patients (18.0%) died in Group C. Table 5 shows the causes of death in those subjects. The most frequent cause of death was infectious complications. The second was respiratory failure. The rate of infection was the highest in Group C, because infection as a cause of death was frequent in the early phase of treatment. Figure 1A shows the results of a Kaplan–Meier analysis of patient survival. Patient survival was significantly improved in Group C compared to that in Group A ($p < 0.05$). The six-month survival rate was 79.2%, that for 12 months was 75.5%, and that for 24 months was 72.0% in Group A. The corresponding values for Group B were 80.1, 78.3, and 72.8%, respectively. In Group C, they were 86.1, 82.8, and 77.7%, respectively.

Table 6 shows the survival rates in patients with each type of RPGN. Patients with RLV and MPA showed a significant improvement in survival in Group C, whereas patients with other types of RPGN did not.

Figure 1B shows the results of a Kaplan–Meier analysis of renal survival. Renal survival was significantly improved in Groups B and C compared to Group A ($p < 0.05$). The six-month survival rate was 73.2%, that at 12 months was 71.9%, and that at 24 months was 68.7% in Group A. The corresponding values in Group B were 81.3,

**Table 2** Sex and age distribution of RPGN cases at presentation

| | Group A | | | | Group B | | | | Group C | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male (%) | Mean age | SD | Age range | Male (%) | Mean age | SD | Age range | Male (%) | Mean age | SD | Age range |
| Primary | | | | | | | | | | | | |
| Crescentic GN | | | | | | | | | | | | |
| Anti-GBM antibody-associated crescentic GN | 48.8 | 52.05 | 16.51 | 10–79 | 45.0 | 54.83 | 18.82 | 19–83 | 40.9 | 61.59 | 18.34 | 11–77[b,c] |
| Immune-complex-associated crescentic GN | 53.9 | 54.27 | 18.66 | 14–77 | 66.7 | 70.00 | 9.09 | 60–82 | 50.0 | 51.50 | 24.82 | 11–75 |
| Renal-limited vasculitis | 44.6 | 61.85 | 14.95 | 6–88 | 54.3 | 64.98 | 14.13 | 13–91 | 50.0 | 67.28 | 13.12 | 1–92[a,b,c] |
| Overlapped crescentic GN | 44.4 | 60.84 | 15.61 | 6–82 | 20.0 | 64.80 | 9.20 | 50–73 | 42.9 | 51.29 | 26.24 | 8–72 |
| Undifferentiated primary crescentic GN | 69.3 | 56.62 | 23.92 | 8–84 | 0.0 | 73.00 | 14.00 | 59–87 | 50.0 | 63.36 | 15.29 | 29–81 |
| Primary GN with crescents | | | | | | | | | | | | |
| Mesangioproliferative glomerulonephritis | 77.8 | 50.56 | 26.50 | 6–75 | 100.0 | 71.50 | 6.50 | 65–78 | 100.0 | 74.75 | 1.30 | 73–76 |
| Membranous nephropathy | 50.0 | 59.00 | 3.00 | 56–62 | 50.0 | 41.00 | 27.00 | 14–68 | 100.0 | 21.00 | 0.00 | 21–21 |
| IgA nephropathy | 70.8 | 40.32 | 19.38 | 8–75 | 77.8 | 56.11 | 14.39 | 31–77 | 75.0 | 42.78 | 26.03 | 8–78[a] |
| Non-IgA mesangial proliferative GN | 33.3 | 53.75 | 14.15 | 30–65 | 50.0 | 40.00 | 30.00 | 10–70 | 100.0 | 64.00 | 1.00 | 63–65 |
| Other primary GN | 100.0 | 60.50 | 3.50 | 57–64 | | | | | 0.0 | 3.00 | 0.00 | 3–3 |
| Systemic disease-associated | | | | | | | | | | | | |
| Goodpasture's syndrome | 42.9 | 54.36 | 15.46 | 23–76 | 60.0 | 62.20 | 9.43 | 45–72 | 75.0 | 70.88 | 10.64 | 57–93[b,c] |
| Systemic lupus erythematosus | 34.0 | 35.84 | 14.55 | 13–72 | 0.0 | 55.80 | 11.03 | 44–75 | 36.4 | 46.73 | 19.04 | 15–75[a,b,c] |
| Wegener's granulomatosis | 59.1 | 46.68 | 17.36 | 16–85 | 66.7 | 57.11 | 12.15 | 77–32 | 57.1 | 55.71 | 18.21 | 14–80 |
| Microscopic polyangiitis | 47.1 | 64.60 | 11.98 | 7–87 | 39.7 | 65.14 | 16.08 | 5–91 | 49.5 | 68.77 | 12.00 | 7–88[b,c] |
| Other necrotizing vasculitis | 50.0 | 60.67 | 9.83 | 75–47 | 20.0 | 52.00 | 21.42 | 14–79 | 75.2 | 69.25 | 14.55 | 46–83 |
| Purpura nephritis | 55.6 | 45.83 | 19.98 | 11–75 | 20.0 | 39.40 | 24.30 | 11–77 | 61.5 | 52.33 | 28.35 | 5–82 |
| Cryoglobulinemia | 20.0 | 60.00 | 9.06 | 51–77 | 33.3 | 58.00 | 12.19 | 47–75 | 50.0 | 56.75 | 23.25 | 17–74 |
| Rheumatoid arthritis | 33.3 | 58.33 | 13.25 | 22–77 | 0.0 | 68.50 | 10.50 | 58–79 | 0.0 | 64.50 | 7.40 | 52–70 |
| Malignant neoplasm | 100.0 | 62.50 | 3.50 | 59–66 | 0.0 | 59.00 | 0.00 | 59–59 | | | | |
| Other systemic diseases | 27.3 | 41.00 | 21.80 | 3–72 | 11.1 | 54.22 | 13.02 | 20–67 | 22.2 | 62.22 | 9.35 | 47–75[b,c] |
| Infection-associated | | | | | | | | | | | | |
| Poststreptococcal acute glomerulonephritis | 75.0 | 42.38 | 23.53 | 7–84 | 0.0 | 76.50 | 4.50 | 72–81 | | | | |
| Abscess | 100.0 | 73.00 | 0.00 | 73–73 | 50.0 | 32.50 | 16.50 | 16–49 | 33.3 | 47.33 | 17.75 | 31–72 |
| Hepatitis C virus | 100.0 | 68.00 | 0.00 | 68–68 | 100.0 | 71.00 | 0.00 | 71–71 | | | | |
| Other infectious diseases | 92.3 | 54.92 | 15.95 | 25–78 | 100.0 | 60.50 | 9.50 | 51–70 | 80.0 | 63.60 | 8.14 | 54–72 |
| Drug-associated | 28.6 | 54.29 | 13.20 | 36–77 | 0.0 | 64.00 | 0.00 | 64–64 | 100.0 | 80.00 | 1.00 | 79–81[b,c] |
| Others | 28.6 | 43.29 | 21.36 | 2–78 | 0.0 | 64.00 | 0.00 | 64–64 | 55.6 | 51.78 | 28.01 | 2–78 |
| Unknown | 39.3 | 59.89 | 20.82 | 5–83 | 50.0 | 66.64 | 10.41 | 56–91 | 29.7 | 64.03 | 16.20 | 4–80[c] |
| Total | 48.5 | 57.47 | 17.96 | 2–88 | 47.4 | 62.80 | 15.93 | 5–91 | 48.5 | 64.72 | 16.56 | 1–93[a,b,c] |

[a] $p < 0.05$ between Groups A and B

[b] $p < 0.05$ between Groups A and C

[c] $p < 0.05$ between Groups B and C

78.6, and 75.4%, respectively. In Group C, they were 81.8, 80.5, and 76.7%, respectively.

Table 7 shows the renal survival rate for each type of RPGN. Patients with RLV and MPA showed a significant improvement in survival in Groups B and C compared to Group A. However, renal survival in patients with Goodpasture's syndrome showed a significant exacerbation in Groups B and C in comparison with Group A.

For immunosuppressive treatment as an initial treatment, rates of cyclophosphamide administration (Group A: 22.5%, Group B: 26.6%, and Group C: 21.5%) or methyl prednisolone administration (Group A: 69.5%, Group B: 68.5%, and Group C: 70.4%) were not different during our observation period. However, the initial dose of oral predonisolone showed a significant reduction in Groups B and C compared to Group A in RLV (Group A: 0.81 ± 0.26 mg/kg/day, Group B: 0.73 ± 0.22 mg/kg/day, and Group C: 0.71 ± 0.24 mg/kg/day) and in MPA (Group A: 0.91 ± 0.29 mg/kg/day, Group B: 0.81 ± 0.28 mg/kg/day, and Group C: 0.75 ± 0.24 mg/kg/day, respectively).

**Table 3** Clinical characteristics at presentation

| | Serum creatinine (mg/dl) | | Urinary protein (g/day) | | CRP (mg/dl) | | Hemoglobin (g/dl) | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Primary | | | | | | | | |
| Anti-GBM antibody-associated crescentic GN | | | | | | | | |
| Group A | 6.7 | 4.2 | 2.3 | 2.8 | 8.6 | 8.8 | 9.5 | 1.9 |
| Group B | 7.6 | 7.6 | 3.5 | 2.8 | 9.6 | 9.3 | 9.2 | 1.9 |
| Group C | 4.8 | 3.4 | 1.3[c] | 0.7 | 10.3 | 8.3 | 9.6 | 2.1 |
| Immune-complex-associated crescentic GN | | | | | | | | |
| Group A | 4.8 | 3.4 | 1.5 | 1.1 | 3.8 | 3.7 | 9.4 | 2.2 |
| Group B | 3.1 | 0.3 | 3.4 | 2.8 | 1.6 | 1.5 | 9.6 | 1.8 |
| Group C | 1.9 | 1.2 | 4.0[b] | 3.2 | 3.8 | 4.6 | 11.3 | 2.2 |
| Pauci-immune crescentic GN | | | | | | | | |
| Group A | 4.7 | 3.5 | 1.9 | 1.9 | 5.1 | 5.6 | 9.2 | 2.2 |
| Group B | 3.6 | 2.7 | 2.4 | 2.8 | 5.1 | 5.0 | 9.4 | 2.2 |
| Group C | 3.7[a,b] | 2.8 | 2.0[a] | 1.7 | 5.3 | 5.2 | 9.5 | 2.0 |
| Primary GN with crescents | | | | | | | | |
| Group A | 6.3 | 3.0 | 4.7 | 1.3 | 2.4 | 2.1 | 9.8 | 0.8 |
| Group B | 4.8 | 4.6 | 3.9 | 3.7 | 3.6 | 5.2 | 10.4 | 2.7 |
| Group C | 4.1 | 3.4 | 3.7 | 3.1 | 4.3 | 7.3 | 9.9 | 2.7 |
| Systemic disease associated | | | | | | | | |
| Goodpasture's syndrome | | | | | | | | |
| Group A | 7.0 | 4.6 | 3.7 | 2.6 | 8.6 | 8.1 | 8.8 | 2.0 |
| Group B | 9.5 | 4.1 | 1.0 | 0.0 | 25.1 | 11.4 | 9.4 | 1.9 |
| Group C | 6.4 | 2.9 | 2.4 | 1.6 | 16.8[a,b] | 7.2 | 10.3 | 1.3 |
| Systemic lupus erythematosus | | | | | | | | |
| Group A | 2.4 | 1.8 | 5.3 | 3.9 | 2.5 | 5.9 | 9.0 | 2.0 |
| Group B | 3.1 | 1.6 | 4.8 | 3.0 | 1.2 | 0.8 | 9.6 | 0.9 |
| Group C | 1.9 | 1.5 | 1.6[b] | 1.4 | 1.9 | 2.2 | 9.5 | 2.3 |
| Wegener's granulomatosis | | | | | | | | |
| Group A | 4.5 | 5.3 | 0.9 | 0.4 | 10.3 | 9.7 | 9.8 | 1.6 |
| Group B | 4.1 | 4.2 | 0.8 | 0.8 | 10.6 | 4.9 | 9.3 | 2.6 |
| Group C | 3.0 | 2.6 | 1.2 | 0.8 | 7.4 | 6.2 | 10.1 | 2.0 |
| Microscopic polyangiitis | | | | | | | | |
| Group A | 4.5 | 3.2 | 1.6 | 2.8 | 9.5 | 7.8 | 9.0 | 1.9 |
| Group B | 3.4 | 2.7 | 1.6 | 4.0 | 9.2 | 6.1 | 8.9 | 1.9 |
| Group C | 3.3[a,b] | 2.4 | 1.4 | 1.4 | 7.5[b] | 6.7 | 9.2 | 1.9 |
| Total | | | | | | | | |
| Group A | 4.4 | 3.5 | 2.2 | 2.7 | 6.3 | 7.0 | 9.4 | 2.1 |
| Group B | 3.9 | 3.6 | 2.5 | 3.2 | 6.2 | 6.5 | 9.3 | 2.3 |
| Group C | 3.6[a,b] | 2.8 | 2.0 | 2.0 | 6.2 | 6.4 | 9.6 | 2.1 |

*GN* glomerulonephritis

[a] $p < 0.05$ between Groups A and B

[b] $p < 0.05$ between Groups A and C

[c] $p < 0.05$ between Groups B and C

## Prognostic factors and clinical grading

Age (<59, 60–69, >70), serum creatinine (<3.0, 3.0–6.0, ≥6.0 mg/dl), proteinuria (>1.5 g/day), serum albumin (≥3.0 g/dl), C-reactive protein (<2.6, 2.6–10, ≥10 mg/dl), presence of lung involvement and systolic blood pressure (>140 mmHg) are a significant prognostic factors for predicting patient survival in Group A according to the chi-square test ($p < 0.05$). We selected age, serum creatinine, C-reactive protein, and presence of lung involvement as strong independent prognostic factors ($p < 0.01$) by using a Cox regression model in Group A. We created an RPGN grading system based on these four values. Every subject was categorized into four clinical grades by summing the four prognostic factor scores (Table 8). Figure 2A shows the results of a Kaplan–Meier analysis of

**Table 4** Positive rate of MPO-ANCA and PR3-ANCA

| | RLV | | MPA | | Wegener's granulomatosis | |
|---|---|---|---|---|---|---|
| | *n* (tested) | Positive rate (%) | *n* (tested) | Positive rate (%) | *n* (tested) | Positive rate (%) |
| MPO-ANCA | | | | | | |
| Group A | 326 | 86.8 | 143 | 94.4 | 21 | 28.6 |
| Group B | 149 | 83.2 | 58 | 86.2 | 9 | 0.0 |
| Group C | 248 | 92.7 | 129 | 91.5 | 14 | 28.6 |
| Total | 723 | 88.1 | 330 | 91.8 | 44 | 22.7 |
| PR3-ANCA | | | | | | |
| Group A | 321 | 10.6 | 135 | 5.2 | 22 | 68.2 |
| Group B | 143 | 6.3 | 55 | 7.3 | 9 | 88.9 |
| Group C | 240 | 3.8 | 121 | 6.6 | 14 | 64.3 |
| Total | 704 | 7.4 | 311 | 6.1 | 45 | 71.1 |

**Table 5** Cause of death

| | Group A | | Group B | | Group C | |
|---|---|---|---|---|---|---|
| *n* | 884 | | 321 | | 568 | |
| Deceased patients, *n*, % | 351 | 39.71% | 110 | 34.27% | 102 | 17.96% |
| Mean observation period, month (range) | 59.4 | (0.0–13.6) | 36.8 | (0.0–98.8) | 17.5 | (0–59.2) |
| Infection | 169 | 48.1% | 42 | 38.2% | 57 | 55.9% |
| Respiratory failure | 102 | 29.1% | 27 | 24.5% | 25 | 24.5% |
| Interstitial pneumonitis | 37 | 10.5% | 16 | 14.5% | 20 | 19.6% |
| Pulmonary bleeding | 48 | 13.7% | 8 | 7.3% | 12 | 11.8% |
| Cerebral hemorrhage | 22 | 6.3% | 6 | 5.5% | 6 | 5.9% |
| Congestive heart failure | 35 | 10.0% | 14 | 12.7% | 6 | 5.9% |
| Myocardial infarction | 3 | 0.9% | 6 | 5.5% | 1 | 1.0% |
| Gastrointestinal bleeding | 33 | 9.4% | 15 | 13.6% | 7 | 6.9% |

patient survival in Group A patients by clinical grading category. Six-month survival of Group A patients with grade I was 89.3%, grade II was 77.3%, grade III was 62.1%, and grade IV was 52.4%. Using this grading system, we can predict not only short-term prognosis but also long-term prognosis. In the Group B and Group C patients, this clinical grading system can predict both short and long-term patient prognosis very well (Fig. 2B, C).

## Discussion

In 1998, we started this survey of RPGN cases because we had no epidemiological data on RPGN in Japan, and even though the number of RPGN patients is increasing, the number of cases of RPGN that are found in a single nephrology department annually are limited. During the early years of this study, we felt that the prognosis of RPGN patients in Japan was very poor compared to other races and countries. We started to analyze the etiology of this.

Couser [9] proposed a classification of RPGN based on immunofluorescence microscopy findings, and reported the proportions of patients with RPGN to be 20% for linear (anti-GBM antibody), 40% for granular (immune complex) and 40% for pauci-immune (idiopathic) types in 1988. Since the discovery of ANCA as a marker of idiopathic pauci-immune crescentic GN (namely RLV) as well as MPA [10–12], the proportion of pauci-immune-type RPGN patients has increased. This increment was also observed when the age of subjects increased [13]. The immunofluorescence microscopy findings in our subjects consisted of 64.0% with pauci-immune, approximately 20.0% with granular, and 6.1% with linear patterns. Those proportions were almost constant during our observation period. Considering the age of our subjects, the rate of immunofluorescence microscopy findings was almost the same as those in previous reports [13]. However, the prevalences of both

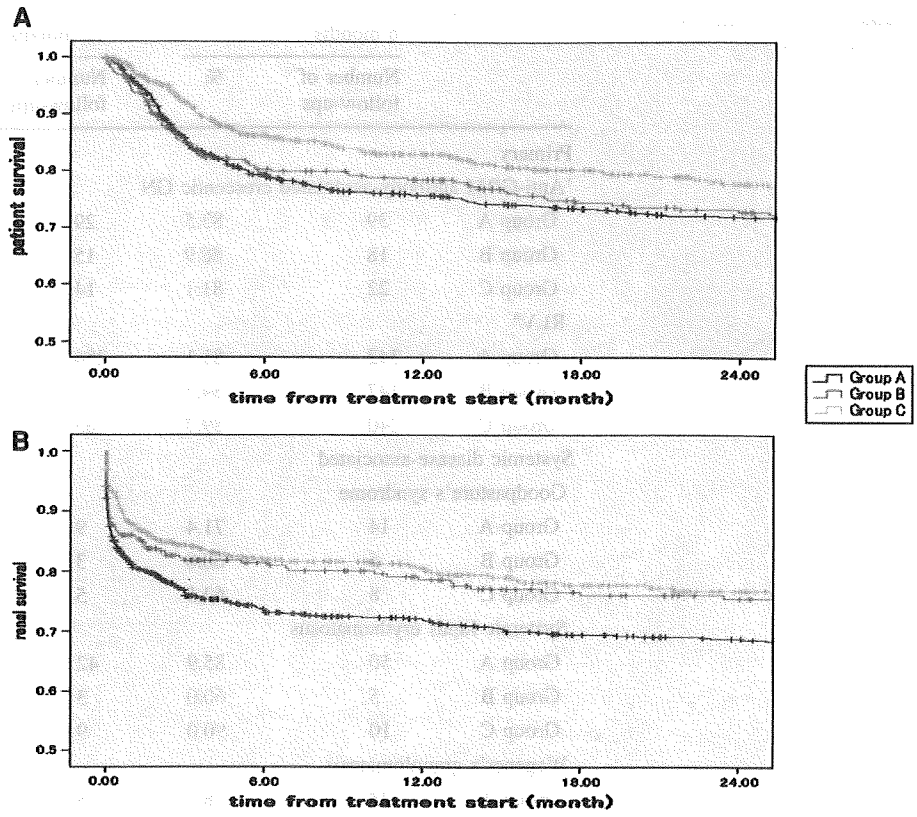


**Fig. 1** Patient survival and renal survival of RPGN patients in Japan. **a** Patient survival was significantly improved in Group C compared to Groups A and B. **b** Renal survival was significantly improved in Groups B and C compared to Group A

MPO-ANCA and PR3-ANCA were quite different. Others reported that the proportion of PR3-ANCA-positive patients in pauci-immune crescentic GN or MPA was 28–50% [5, 14]. MPO-ANCA-positive patients showed a slower deterioration of renal function, were predominantly female, and were older than PR3-ANCA-positive patients [14]. From previous reports, the mean age ranged from 45 to 56 years in PR3-ANCA-positive patients and from 57 to 63 years in MPO-ANCA-positive patients [14]. The reason for the predominance of MPO-ANCA may be related to the older age at presentation of our RPGN patients. Although a recent increase in the average age was observed in patients with MPA, the prevalence of MPO-ANCA-positive patients decreased slightly. Furthermore, several reports have suggested that susceptibility to MPO-ANCA-associated vasculitis is related to environmental factors such as air pollution [15] and exposure to silica [16], latitude [17], or genetic factors such as polymorphism of the *CD18* gene [18] and HLA-DRB1*0901 [19]. Further investigations are needed to clarify racial and demographic differences associated with the prevalence of MPO-ANCA-associated vasculitis.

The RPGN patients included in our study often died due to infectious complications. Gayraud et al. [20] reported that patients older than 65 years treated for MPA with corticosteroid and cyclophosphamide often died due to infectious complications compared with those receiving corticosteroid alone. Booth et al. [21] also reported that treatment with cyclophosphamide often induced leukopenia and was strongly associated with sepsis, and sepsis was a determinant of survival.

In 2002, we published a Japanese version of the RPGN clinical guidelines based on data for 715 RPGN patents collected until 2001, who formed part of the Group A patients in this study [7, 22]. Based on a prognostic analysis of these patients, age, serum creatinine level and CRP level at the start of immunosuppressive treatment, and involvement of lung disease were significant prognostic markers in RPGN patients. In detailed prognostic analysis, we found that treatment with corticosteroids and immunosuppressants had a favorable effect on survival in patients in the $\leq$60 year-old group; however, no additional benefit of immunosuppressants on long-term renal survival in patients in older groups was observed. Further, an initial dose of oral prednisolone of >0.8 mg/kg/day was a significant risk factor for early death [7]. Hauer et al. [24] and Vizjak et al. [23] reported that the renal histology of MPO-ANCA-positive patients showed that diffuse, chronic sclerotic lesions predominated on histologic analysis. Thus, to relieve the inflammatory reaction of patients with MPO-ANCA, a lower dose of oral prednisolone is sufficient. Consequently, we recommended in the clinical guidelines (i) that early diagnosis and referral to nephrologists are important and (ii) mild treatment with a lower dose of oral