A Novel Simpler Histological Classification for Renal Survival in IgA Nephropathy: A Retrospective Study

Carlo Manno, MD, Giovanni F.M. Strippoli, MD, Christian D'Altri, MD, Diletta Torres, MD, Michele Rossini, MD, and Francesco P. Schena, MD, on behalf of the European IgAN Consortium

Background: Patients with immunoglobulin A (IgA) nephropathy may progress to end-stage renal disease (ESRD) within 10 to 20 years after renal biopsy. We evaluated factors associated with long-term renal survival by using a novel simplified histological classification.

Study Design: Retrospective study.

Setting & Participants: 437 patients (296 men, 141 women) with IgA nephropathy seen at our single center from January 1971 to December 2006. Most patients received treatment with renin-angiotensin system inhibitors.

Predictors: Baseline age, sex, presence of hematuria, presence of hypertension, serum creatinine level, urine protein at baseline, and 2 histological classifications.

Outcomes & Measurements: Relationship of baseline factors to time to ESRD was evaluated by means of univariate and multivariate analysis with log-rank test and the Cox proportional hazard method.

Results: In a mean follow-up of 107.6 months, 72 ESRD events occurred. The 5-, 10-, 15-, and 20-year renal survival rates after renal biopsy were 94.1%, 82.1%, 73.1%, and 60.3%, respectively. Independent baseline predictors of increased ESRD risk were microhematuria with absence of recurrent macrohematuria (adjusted hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.30 to 3.65; $P = 0.003$), 1.0 mg/dL (88.4 μmol/L) higher serum creatinine level (HR, 1.50; 95% CI, 1.10 to 2.07; $P = 0.013$), proteinuria with 1.0 g/dL (10.0 g/L) greater protein (HR, 1.28; 95% CI, 1.07 to 1.52; $P = 0.006$), and grading of histological lesions. A 1-grade increase according to our 3-grade classification was associated with a nearly 6-fold ESRD risk increase (adjusted HR, 5.95; 95% CI, 3.54 to 10.01; $P < 0.0001$).

Limitations: Lack of adjustment for changes in treatment that may have occurred during the study period.

Conclusions: Renal damage progression in patients with IgA nephropathy was associated with microscopic hematuria at clinical onset, increased serum creatinine level, increased proteinuria, and grading of histological lesions. Our classification system appears simpler than other classifications and is associated with ESRD risk, which could help identify individual high-risk patients and stratify patients enrolled in randomized clinical trials into homogeneous groups.

Am J Kidney Dis 49:763-775.

INDEX WORDS: Immunoglobulin A (IgA) nephropathy; histological classification; renal survival.

Primary immunoglobulin A (IgA) nephropathy occurs worldwide and is characterized by recurrent episodes of macroscopic hematuria (which usually arise during upper respiratory tract infections) or asymptomatic persistent microscopic hematuria with or without proteinuria. Few epidemiological studies examined the incidence of primary IgA nephropathy in various populations around the world.[1-4] National renal biopsy registries showed that IgA nephropathy is the most common form of primary glomerulonephritis worldwide (30% to 40% of all biopsy-proven primary glomerulonephritis),[5-11] with an incidence ranging from 8.4 to 11.1 cases per million population in Italy[5,10-11] compared with 5.4 to 12.4 per million population in central and

From the Department of Emergency and Organ Transplantation, Renal, Dialysis and Transplant Unit, University of Bari, Bari, Italy.

Received October 9, 2006; accepted in revised form March 19, 2007.

Originally published online as doi:10.1053/j.ajkd.2007.03.013 on May 3, 2007.

Support: This study was partially supported by grants from the 5th European Framework Programme (QLG1-CT-2000-00464), Ministero dell'Università e Ricerca (PRIN 2001-067748 and FIRB 2001-RBNEO13JYM), and Ministero della Salute (RC2006). Potential conflicts of interest: None.

Address correspondence to Francesco P. Schena, MD, Department of Emergency and Organ Transplantation, Renal, Dialysis and Transplant Unit, University of Bari, Piazza Giulio Cesare, 11, 70124, Bari, Italy. E-mail: fp.schena@nephro.uniba.it

0272-6386/07/4906-0007$32.00/0

doi:10.1053/j.ajkd.2007.03.013

eastern Kentucky (United States)[12] and 26 patients per million population in Cotes d'Armor (France).[13] Although initially believed to represent a benign condition,[14] IgA nephropathy is now recognized as a cause of end-stage renal disease (ESRD) in a substantial proportion of patients within 10 to 20 years from its apparent onset.[2] The clinical course is extremely variable and ranges from asymptomatic microscopic hematuria to rapidly progressive renal failure.

Certain renal lesions were associated in some studies with poorer renal prognosis, and several morphological classifications were adopted. The use of different types of classifications is responsible in part for existing controversies in the assessment of rates of progression to ESRD and other renal outcomes. In general, histological grading mainly was based on the presence of cellular proliferation, glomerulosclerosis, crescents, and tubulointerstitial damage. Despite assessment and validation in a cohort of only 20 patients, the most widely adopted classification was that developed by Lee et al,[15] which includes 5 histological grades of disease. This classification was revised subsequently by Haas,[16] who suggested that the classification of Lee et al[15] underscored tubulointerstitial damage. Even the revised classification of Haas[16] was validated in a single cohort of only 109 patients.

Single and multicenter biopsy data available from large cohorts of patients with IgA nephropathy allow for more sophisticated testing of the predictive value and validity of the classification of IgA nephropathy for renal outcomes. We updated and simplified the histological classification[17] of IgA nephropathy based on descriptive criteria of renal lesions made by Churg et al[18] and accepted by the World Health Organization and scored renal biopsy specimens of our patients. In this retrospective study, we assembled a large cohort of patients with IgA nephropathy and evaluated factors recorded at the time of renal biopsy and associated with long-term renal survival, then validated this novel simpler classification in predicting renal outcomes.

METHODS

Renal Biopsy

From January 1971 to December 2004, information for 2,710 renal biopsies of native kidneys performed and/or processed in our unit were collected. In 796 of these (29.4%), IgA nephropathy was diagnosed, and a cohort of 437 patients (296 men, 67.7%; 141 women, 32.3%) followed up for more than 1 year in our single center until December 2006 were included in the study population. In our clinical policy, main reasons for performing a renal biopsy were asymptomatic urinary abnormalities (persistent microscopic hematuria and mild to moderate proteinuria), recurrent episodes of macroscopic hematuria, nephrotic syndrome, acute renal failure, or chronic renal insufficiency of unknown origin without severe alterations shown by means of ultrasound imaging. Biopsies were performed at least 30 days after episodes of macroscopic hematuria. The diagnosis of IgA nephropathy was made by the detection of mesangial deposits staining predominantly for IgA with immunofluorescence studies. Patients with systemic lupus erythematosus, Henoch-Schönlein purpura, or chronic liver diseases were excluded. All biopsy specimens were reviewed by 2 separate pathologists masked to patient outcomes and clinical characteristics. Biopsy specimens were scored according to the morphological classification of Lee et al[15] and using our modified classification.[17]

To assess the severity of renal damage, we distinguish 3 grades (Gs): G1 (mild) includes patients with IgA nephropathy with minor or minimal lesions, G2 (moderate) includes patients with focal-segmental or diffuse proliferative glomerulonephritis, and G3 (severe) includes patients with sclerotic lesions in advanced chronic glomerulonephritis or ESRD. Mesangial hypercellularity was scored as follows: mild with more than 3 and 5 or fewer mesangial cells, and moderate-severe with more than 6 mesangial cells on average in at least 2 glomerular lobules. Sclerosis was defined as the obliteration of capillary loops caused by prevalent increase in matrix, capillary tuft adhesion to Bowman capsule, or both. Endocapillary proliferation was defined as obliteration of the capillary tuft by cells (endothelial, mesangial, or inflammatory cells). Biopsy specimens with normal glomeruli or glomeruli with only a mild increase in mesangial cellularity and no tubulointerstitial changes were assigned to grade G1. The presence of even only 1 glomerulus with segmentally sclerotic lesion excluded a case from being assigned to this grade. Biopsy specimens were assigned to grade G2 if 1 of the following signs was detected: moderate increase in mesangial cellularity (focal or diffuse), endocapillary proliferation, cellular crescents (up to 50% of glomeruli involved), segmental sclerosis, tubular atrophy, and interstitial fibrosis (up to one third of the cortical area). Biopsy specimens were assigned to grade G3 if cellular crescents were present in greater than 50% of glomeruli and/or fibrous crescents or global glomerulosclerosis were present in greater than one third of glomeruli and/or segmentally sclerotic lesions involved greater than 50% of glomeruli (ie, diffuse) and/or tubular atrophy and interstitial fibrosis involved greater than one third of cortical areas. Essential features of the 5- and 3-grade systems used for comparison are listed in Table 1. Patients followed up for at least 1 year, with an average follow-up for the entire cohort of 9 years, were included in the study.

Table 1. Lee's Classification and the 3-Grade Classification

Grade	Glomerular Changes	Tubular and Interstitial Changes	Grade	Glomerular Changes	Tubular and Interstitial Changes
I	Mostly normal; occasional slight mesangial thickening (segmental) with or without hypercellularity	Absent	G1 (mild)	Normal glomeruli or slight increase in mesangial matrix and/or cellularity	None
II	Less than half the glomeruli show localized mesangial proliferation and sclerosis; rarely, small crescent	Absent			
III	Diffuse mesangial proliferation and thickening with focal and segmental variation; occasional small crescents and adhesions	Focal interstitial edema and infiltrate occasionally present; tubular atrophy rare	G2 (moderate)	Moderate focal or diffuse mesangial proliferation and/or focal segmental sclerosis and/or endocapillary proliferation and/or cellular crescents up to 50% of glomeruli	Tubular atrophy and interstitial fibrosis up to 1/3 of cortical area
IV	Marked diffuse mesangial proliferation and sclerosis; crescents present in up to 45% of glomeruli; partial or total glomerulosclerosis frequent	Tubular atrophy, interstitial inflammation, and occasional interstitial foam cells			
V	Similar to grade IV, but more severe; crescents present in > 45% of glomeruli	Similar to grade IV, but more severe	G3 (severe)	Cellular crescents in > 50% of glomeruli and/or global glomerulosclerosis or fibrous crescents involving > 1/3 of glomeruli and/or diffuse segmental sclerosis	Tubular atrophy and interstitial fibrosis involving > 1/3 of cortical area

Note: Lee's classification on left and 3-grade classification on right. Mesangial hypercellularity was scored as follows: mild (>3 and ≤5 mesangial cells), moderate to severe (≥6 mesangial cells on the average) at least in 2 glomerular lobules. Sclerosis was defined as the obliteration of capillary loops due to prevalent increase in matrix or as capillary tuft adhesion to Bowman capsule or both. Endocapillary proliferation was defined as the obliteration of the capillary tuft by cells (endothelial, mesangial, or inflammatory cells).

Study Factors and Definitions

Demographic, clinical, laboratory, and histological data were recorded in our database, including sex, age at the time of apparent onset of symptoms and at renal biopsy, and type of onset (microscopic or recurrent macroscopic hematuria). Mean arterial pressure, serum creatinine level, estimated creatinine clearance using the Cockcroft-Gault equation, and 24-hour urinary protein excretion were considered at the time of renal biopsy. No missing data were present and handled. Asymptomatic persistent microhematuria (>5,000 red blood cells/mL in urine) without episodes of macrohematuria sometimes was detected by chance as a result of screening for preemployment, sport activities, or blood donation. Usually microhematuria was accompanied by mild proteinuria (urinary protein excretion, 0.1 to 0.9 g/24 h), rarely by moderate (1.0 to 2.9 g/24 h) or severe proteinuria (≥3.0 g/24 h). The number of recurrent episodes of macrohematuria was variable, usually occurred during upper respiratory tract infections, and persisted for less than 3 days; urine color was red or brown and blood casts were common. Mean arterial pressure of 107 mm Hg or greater was regarded as hypertension according to World Health Organization crite-

ria. All exposure and outcome data were double-entered in a relational database. Data entry was checked by a third investigator at the time of data analysis.

Study Outcome

The study end point was progression of renal disease estimated on the basis of ESRD and evaluated as the need for regular dialysis treatment or renal transplantation. In our monocentric study, the same criteria were applied to all patients with a creatinine clearance less than 5 mL/min (<0.08 mL/s) and/or with uremic symptoms.

Regulatory Considerations

The study was performed according to recommendations outlined in the Declaration of Helsinki (IV Adaptation). Each patient who underwent renal biopsy in our institution was informed of the expected benefits and potential risks associated with the procedure and agreed to anonymous use of collected data for future descriptive or inferential statistical analyses, providing an informed consent.[19]

Statistical Analysis

Continuous data were analyzed descriptively using mean ± SD or median and interquartile range, and categorical data were described as integers, frequencies, and percentages, as appropriate. Baseline characteristics of individuals affected by IgA nephropathy were compared using 1-way analysis of variance, Kruskal-Wallis test, unpaired Student *t*-test, and Mann-Whitney U test as appropriate for continuous data and chi-square statistic for categorical data. Univariate and multivariate analyses of renal survival were carried out based on the end point of ESRD or renal transplantation. Potential nonlinear effects of exposure factors were explored as appropriate and reported if identified. Cumulative renal survival and its 95% confidence interval (CI) from the time of renal biopsy was analyzed by means of Kaplan-Meier curves for censored data. Differences between groups were compared using log-rank test.

Univariate and multivariate analysis based on the Cox regression proportional hazard method was used to assess the relative risk of reaching the outcome of ESRD based on the influence of baseline prognostic factors (age, sex, presence of hematuria [micro or macro], presence of hypertension, serum creatinine level, urinary protein excretion, and the 3-[17] and 5-grade[15] histological classification systems). Variables that could significantly predict ESRD on univariate analysis ($P < 0.05$ or clinical relevance) were used to construct a multivariate Cox model. The final model of adequate statistical power was constructed by means of backward and stepwise approaches to check for consistency, with covariates averaged at baseline. Finally, goodness of fit was tested. Risk estimates are presented as unadjusted and adjusted hazard ratios (HRs) and their 95% CIs, calculated by using an estimated regression coefficient and its SE in the Cox regression analysis. Wald test was used to establish the hierarchy of prognostic factors. All analyses were performed using SAS, version 8.1 (SAS Institute, Cary, NC), and SPSS for Windows, release 12.0 (SPSS Inc, North Sydney, Australia). *P* less than 0.05 is considered statistically significant.

Table 2. Demographic and Clinical Characteristics of Patients With IgA Nephropathy in Our Study Cohort

Characteristic	Measure
No. of patients	437
Age at renal biopsy (y)	31.0 ± 11.4
Age at apparent onset (y)	27.0 ± 10.7
Sex (men)	296 (68)
Onset type (microhematuria)	184 (42)
Mean arterial pressure (mm Hg)	97.8 ± 10.2
Arterial hypertension (yes)	165 (38)
Receiving ACE inhibitors or ARBs (yes)*	306 (70)
Serum creatinine (mg/dL)	1.0 (0.9-1.3)
Creatinine clearance (mL/min)	92.2 ± 29.9
Proteinuria (g/24 h)	0.7 (0.3-1.5)
Renal lesions (Lee's classification)	
Grade I	44
Grade II	150
Grade III	159
Grade IV	58
Grade V	26
Renal lesions (new classification)	
G1 (mild)	173
G2 (moderate)	186
G3 (severe)	78
Follow-up (mo)	107.6 ± 63.2

Note: Data expressed as mean ± SD, median (interquartile range), and absolute and percent frequency.

To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4, creatinine clearance in mL/min to mL/s, multiply by 0.01667.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*Indicated by the presence of hypertension or proteinuria with protein greater than 0.5 g/24 h.

RESULTS

Baseline demographic and clinical findings at the time of renal biopsy are listed in Table 2. Mean age at renal biopsy was 31.0 ± 11.4 years. Mean age at apparent onset of disease was 27.0 ± 10.7 years. Average time from onset to biopsy was 4.0 ± 5.7 years. Type of onset was macroscopic hematuria in 253 of 437 patients (57.9%) and persistent microhematuria in 184 of 437 patients (42.1%). Arterial hypertension was present in 165 of 437 patients (37.7%). At renal biopsy, median serum creatinine value was 1.0 mg/dL (interquartile range, 0.9 to 1.3 [88.4 μmol/L]; interquartile range, 79.6 to 114.9]), mean creatinine clearance was 92.2 ± 29.9 mL/min (1.54 ± 0.50 mL/s), median daily proteinuria value was protein of 0.70 g/24 h (interquartile range, 0.30 to 1.50), and mean arterial pressure was 97.8 ± 10.2 mm Hg. At any time during the

Table 3. Demographic and Clinical Characteristics of Subgroups With IgA Nephropathy Considered in This Study With Respect to Histological Lee's Classification

	Grade (Lee's classification)					
	I	II	III	IV	V	*P*
No. of patients	44	150	159	58	26	Not applicable
Age at renal biopsy (y)	27.9 ± 10.3	27.8 ± 9.8	32.6 ± 11.9	35.5 ± 12.0	34.2 ± 12.6	<0.0001
Age at apparent onset (y)	25.9 ± 9.1	24.8 ± 9.9	27.8 ± 11.2	30.4 ± 11.5	30.6 ± 10.3	0.0018
Sex (men)	31 (70)	92 (61)	109 (69)	47 (81)	17 (65)	0.100
Onset type (microhematuria)	13 (30)	52 (35)	69 (43)	32 (55)	18 (69)	0.001
Mean arterial pressure (mm Hg)	93.8 ± 8.3	93.2 ± 8.6	97.9 ± 8.7	108.5 ± 7.8	110.2 ± 8.2	<0.0001
Arterial hypertension (yes)	10 (23)	34 (23)	64 (40)	40 (69)	17 (65)	<0.0001
Serum creatinine (mg/dL)	0.9 (0.7-1.1)	0.9 (0.8-1.0)	1.0 (0.9-1.2)	1.5 (1.1-1.9)	2.2 (1.4-3.2)	<0.0001
Creatinine clearance (mL/min)	109.9 ± 19.1	104.6 ± 24.4	93.9 ± 25.8	71.6 ± 27.1	48.2 ± 25.1	<0.0001
Proteinuria (g/24 h)	0.2 (0.2-0.7)	0.3 (0.2-0.6)	1.0 (0.4-1.6)	1.8 (1.0-2.4)	1.9 (1.3-3.4)	<0.0001
ACE inhibitor or ARB therapy (yes)	25 (57)	101 (66)	124 (78)	42 (72)	15 (58)	0.08

Note: Data expressed as mean ± SD, median (interquartile range), and absolute and percent frequency. Comparisons between groups were made by means of 1-way analysis of variance, Kruskal-Wallis test, or chi-square test. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4, creatinine clearance in mL/min to mL/s, multiply by 0.01667.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

study observation period, hypertensive patients and those with proteinuria with protein greater than 0.5 g/24 h received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and no patient was treated with steroids or cytotoxic drugs.

The distribution of histological lesions according to Lee's classification was as follows: grade I, 44 patients (10.1%); grade II, 150 patients (34.3%); grade III, 159 patients (36.4%); grade IV, 58 patients (13.2%); and grade V, 26 patients (6.0%). Baseline demographic and clinical findings according to the 5 different histological grades at the time of renal biopsy are listed in Table 3. There was a significant difference among groups for age at renal biopsy ($P < 0.0001$), age at apparent onset ($P < 0.0001$), type of onset of disease ($P < 0.001$), proportion of patients with arterial hypertension ($P < 0.0001$), median values for serum creatinine and daily proteinuria, and mean creatinine clearance ($P < 0.0001$). According to our novel and simpler 3-grade classification, the distribution of histological lesions was as follows: 173 patients (39.6%) with mild renal damage (G1), 186 patients (42.6%) with moderate renal damage (G2), and 78 patients (17.8%) with severe renal damage (G3). Baseline demographic and clinical findings according to the 3 different histological grades at the time of renal biopsy are listed in Table 4. There was a significant difference among groups for age at renal biopsy ($P < 0.0001$), age at apparent onset ($P < 0.001$), type of onset of disease ($P < 0.002$), proportion of patients with arterial hypertension ($P < 0.0001$), median values for serum creatinine and daily proteinuria, and mean creatinine clearance ($P < 0.0001$).

Renal Survival

During a mean follow-up of 107.6 ± 63.2 months, 72 ESRD events occurred. The 5-, 10-, 15-, and 20-year renal survival rates in all patients from time of renal biopsy were 94.1% (patients at risk, 349), 82.1% (patients at risk, 152), 73.1% (patients at risk, 53), and 60.3% (patients at risk, 24), respectively. No patient died before ESRD during the study observation period. As shown in Fig 1A, the cumulative probability of ESRD was greater in patients with grades IV and V histological lesions compared

Table 4. Demographic and Clinical Characteristics of Subgroups With IgA Nephropathy Considered in This Study With Respect to 3-Grade Histological Classification

Grade (new classification)	G1	G2	G3	*P*
No. of patients	173	186	78	Not applicable
Age at renal biopsy (y)	27.8 ± 9.9	32.7 ± 11.9	34.1± 11.5	<0.0001
Age at apparent onset (y)	24.7 ± 9.7	28.1 ± 11.5	29.5 ± 10.1	0.001
Sex (men)	105 (62)	129 (69)	62 (79)	0.011
Onset type (microhematuria)	57 (33)	83 (45)	44 (56)	0.002
Mean arterial pressure (mm Hg)	93.5 ± 8.2	98.1 ± 8.4	109.2 ± 8.0	<0.001
Arterial hypertension (yes)	34 (20)	73 (39)	58 (74)	<0.0001
Serum creatinine (mg/dL)	0.9 (0.8-1.0)	1.0 (0.9-1.2)	1.5 (1.3-2.6)	<0.0001
Creatinine clearance (mL/min)	105.4 ± 23.3	96.2 ± 25.7	59.7 ± 25.7	<0.0001
Proteinuria (g/24 h)	0.3 (0.2-0.6)	1.0 (0.4-1.6)	1.8 (1.0-2.9)	<0.0001
ACE inhibitor or ARB therapy (yes)	105 (61)	135 (72)	57 (73)	0.07

Note: Data expressed as mean ± SD, median (interquartile range), and absolute and percent frequency. Comparisons between groups were made by means of 1-way analysis of variance, Kruskal-Wallis test, or chi-square test. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4, creatinine clearance in mL/min to mL/s, multiply by 0.01667.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

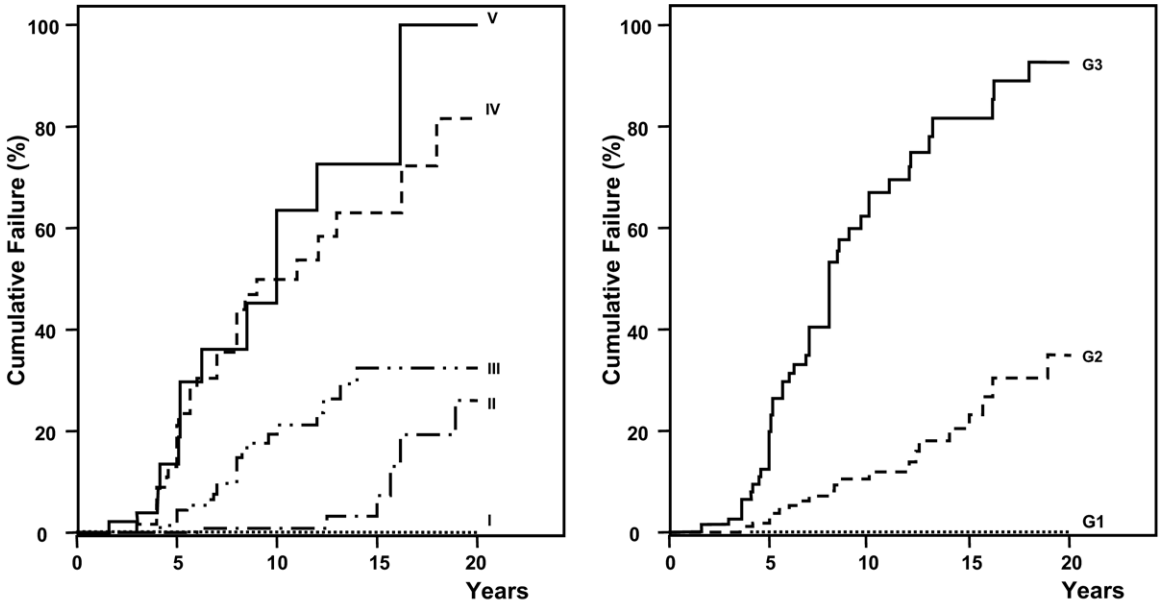
with those with grades I, II, and III (log-rank test, chi-square 113.2; $P < 0.0001$) according to Lee's classification. Furthermore, the cumulative probability of ESRD was greater in patients with severe lesions (G3) than those with moderate (G2) and mild renal damage (G1) according to our 3-grade classification system (log-rank test, chi-square 179.7; $P < 0.0001$; Fig 1B). The distribution of ESRD events in patients according to 5 and 3 categories of histological classification are listed in Table 5.

Unadjusted and adjusted HR estimates of the association between these different risk factors and ESRD are reported in 2 different models. In each analysis, 7 variables at the time of renal biopsy (age, sex, microhematuria at onset, arterial hypertension, serum creatinine [milligrams per deciliter], proteinuria [grams of protein per 24 hours], and the 5- [Table 6] or 3-grade [Table 7] systems of histological renal lesions) were included in the multivariate model. There was a strong association between risk of ESRD and presence of microhematuria at onset (adjusted HR, 2.05; 95% CI, 1.22 to 3.44; $P = 0.007$; adjusted HR 2.18, 95% CI 1.30 to 3.65, $P = 0.003$), but no association between the presence of arterial hypertension and risk of ESRD (adjusted HR, 1.64; 95% CI, 0.91 to 2.95; $P = 0.102$; adjusted HR, 1.08; 95% CI, 0.60 to 1.93; $P = 0.802$). In addition, risk of ESRD significantly increased for every 1.0 mg/dL (88.4 μmol/L) increase in serum creatinine level (adjusted HR, 1.77; 95% CI, 1.26 to 2.48; $P = 0.001$; adjusted HR, 1.50; 95% CI, 1.10 to 2.07; $P = 0.013$) and for every 1.0-g/24 h increase in daily proteinuria (adjusted HR, 1.27; 95% CI, 1.07 to 1.50; $P = 0.006$; adjusted HR, 1.28; 95% CI, 1.07 to 1.52; $P = 0.006$).

Finally, with respect to grading of histological lesions on a continuous scale of risk assessment, for every 1-stage increase in degree of disease according to Lee's classification, there was a nearly 2-fold increase in risk of ESRD (adjusted HR, 1.74; 95% CI, 1.29 to 2.34; $P < 0.0001$); for every 1-stage increase in degree of disease according to our simple 3-grade classification system, there was a nearly 6-fold increase in risk of ESRD (adjusted HR, 5.95; 95% CI, 3.54 to 10.01; $P < 0.0001$). Adjusted estimates of renal survival by individual degree of histological lesion are shown in Fig 2. Of note, there was some overlap between survival in patients with grades IV and V disease when we used Lee's classification, but not when we used the new classification.

DISCUSSION

In this study, we tested the value of our novel simpler histological classification of IgA nephropathy in predicting renal outcomes. Baseline demographic and clinical findings of our cohort of 437 patients with IgA nephropathy followed up in a single center differed according to the use of the 5 or 3 histological grades at time of renal biopsy.



At risk (N)					
I	44	38	22	17	5
II	150	123	68	24	10
III	159	128	43	20	8
IV	58	42	13	4	2
V	26	16	5	1	0

Cumulative Failure and 95% CI					
I	0	0	0	0	0
II	0	0	0.9 (0.2-6.0)	7.8 (2.1-26.4)	26.4 (11.6-53.3)
III	0	4.7 (2.1-10.2)	21.9 (14.2-32.9)	33.1 (22.0-47.7)	33.1 (22.1-47.7)
IV	0	21.9 (12.7-36.2)	50.8 (36.5-67.0)	64.2 (47.4-80.6)	82.9 (59.8-96.1)
V	0	13.4 (4.5-36.4)	63.47 (38.6-87.4)	0	0

At risk (N)					
G1	173	139	74	20	7
G2	186	150	63	29	12
G3	78	59	16	5	2

Cumulative Failure and 95% CI					
G1	0	0	0	0	0
G2	0	3.9 (1.8-8.5)	12.3 (7.3-20.4)	23.9 (14.8-37.3)	35.6 (22.5-53.3)
G3	0	20.3 (12.5-31.9)	67.6 (54.5-80.1)	85.8 (72.4-94.8)	92.9 (85.0-98.6)

Figure 1. (A) Cumulative failure estimated by means of Kaplan-Meier methods as a function of histological class (grades I to V) according to Lee's classification. The end point outcome is represented by end-stage renal disease (ESRD) requiring dialysis or transplantation. (B) Cumulative failure estimated by means of Kaplan-Meier methods as a function of histological class (G1 to G3) according to the new classification. The end point outcome is represented by ESRD requiring dialysis or transplantation. Number of patients at risk, numeric values of cumulative failure, and its 95% confidence intervals are reported at the bottom of the figure.

The overall 20-year renal survival rate with ESRD as the end point was 60.3%. The probability of cumulative ESRD was greater in patients with grades IV and V histological lesions compared with those with grades I, II, and III according to Lee's classification. Furthermore, the probability of cumulative ESRD was greater in patients with severe lesions (G3) than those with moderate

Table 5. Distribution of ESRD Events in Patients With IgA Nephropathy According to 5- and 3-Category Histological Classification

Histological Lesions	Grade I	Grade II	Grade III	Grade IV	Grade V	Total
Grade G1	0/42 (0)	0/129 (0)	0/1 (0)	0/0 (0)	0/0 (0)	0/173 (0)
Grade G2	0/2 (0)	7/21 (33)	16/146 (11)	1/18 (6)	0/0 (0)	24/186 (13)
Grade G3	0/0 (0)	0/0 (0)	8/12 (67)	28/40 (70)	12/26 (46)	48/78 (62)
Total	0/44 (0)	7/150 (5)	24/159 (15)	29/58 (50)	12/26 (46)	72/437 (16)

Note: Values expressed as number of ESRD events/number of patients in each category (percent).
Abbreviation: ESRD, end-stage renal disease.

Table 6. Unadjusted and Adjusted Risk Estimates by Means of Cox Proportional Hazard Models for ESRD in 437 Patients With IgA Nephropathy With Respect to Lee's Classification

Risk Factor	Unit of Increase	Unadjusted Risk (HR) (95% CI)	*P*	Adjusted Risk (HR) Without Histological Classification (95% CI)	*P*	Adjusted Risk (HR) With Histological Classification (95% CI)	*P*
Age at renal biopsy (y)	10	1.13 (0.92-1.39)	0.256	0.95 (0.76-1.20)	0.691	0.93 (0.73-1.17)	0.529
Sex (female/male)	0 = F,1 = M	1.51 (0.89-2.58)	0.128	1.05 (0.60-1.85)	0.857	1.14 (0.65-1.99)	0.649
Microhematuria at onset	0 = no, 1 = yes	1.94 (1.21-3.19)	0.005	1.93 (1.16-3.22)	0.012	2.05 (1.22-3.44)	0.007
Arterial hypertension at renal biopsy	0 = no, 1 = yes	4.35 (2.59-7.30)	0.0001	2.12 (1.19-3.79)	0.011	1.64 (0.91-2.95)	0.102
Serum creatinine at renal biopsy (mg/dL)	1	3.29 (2.64-4.10)	0.0001	2.36 (1.75-3.20)	0.0001	1.77 (1.26-2.48)	0.001
Proteinuria at renal biopsy (g/24 h)	1	1.81 (1.59-2.05)	0.0001	1.35 (1.61-1.57)	0.0001	1.27 (1.07-1.50)	0.006
Histological lesions: grade (I-V)	1	2.83 (2.25-3.56)	0.0001			1.74 (1.29-2.34)	0.0001

Note: Basic (initial) – 2 log L = 735.766; Lower (lowest) – 2 log L = 617.467; $P < 0.0001$. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.

(G2) and mild (G1) lesions according to our 3-grade classification system.

Significant predictors of ESRD risk were microscopic hematuria without episodes of macroscopic hematuria at onset of the disease, greater serum creatinine level, greater proteinuria, and histological grading. Risk of ESRD nearly doubled for every unit increase in histological grade according to Lee's classification on a continuous scale, whereas risk increased nearly 6-fold for every unit increase in the degree of disease according to our simpler 3-grade classification system. With a 3-level grading system, risk of ESRD appeared to be greater in patients with microscopic hematuria and proportionally increased for every 1.0 mg/dL (88.4 μmol/L)

Table 7. Unadjusted and Adjusted Risk Estimates by Means of Cox Proportional Hazard Models for ESRD in 437 Patients With IgA Nephropathy With Respect to 3-Grade Classification

Risk Factor	Unit of Increase	Unadjusted Risk (HR) (95% CI)	*P*	Adjusted Risk (HR) Without Histological Classification (95% CI)	*P*	Adjusted Risk (HR) With Histological Classification (95% CI)	*P*
Age at renal biopsy (y)	10	1.13 (0.92-1.39)	0.256	0.95 (0.76-1.20)	0.691	0.92 (0.71-1.17)	0.488
Sex (female/male)	0 = F, 1 = M	1.51 (0.89-2.58)	0.128	1.05 (0.60-1.85)	0.857	0.88 (0.51-1.54)	0.663
Microhematuria at onset	0 = no, 1 = yes	1.94 (1.21-3.19)	0.005	1.93 (1.16-3.22)	0.012	2.18 (1.30-3.65)	0.003
Arterial hypertension at renal biopsy	0 = no, 1 = yes	4.35 (2.59-7.30)	0.0001	2.12 (1.19-3.79)	0.011	1.08 (0.60-1.93)	0.802
Serum creatinine at renal biopsy (mg/dL)	1	3.29 (2.64-4.10)	0.0001	2.36 (1.75-3.20)	0.0001	1.50 (1.10-2.07)	0.013
Proteinuria at renal biopsy (g/24 h)	1	1.81 (1.59-2.05)	0.0001	1.35 (1.61-1.57)	0.0001	1.28 (1.07-1.52)	0.006
Histological lesions (G1-G3)	1	8.47 (5.47-13.11)	0.0001			5.95 (3.54-10.01)	0.0001

Note: Basic (initial) – 2 log L = 735.766; Lower (lowest) – 2 log L = 576.001; $P < 0.0001$. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.

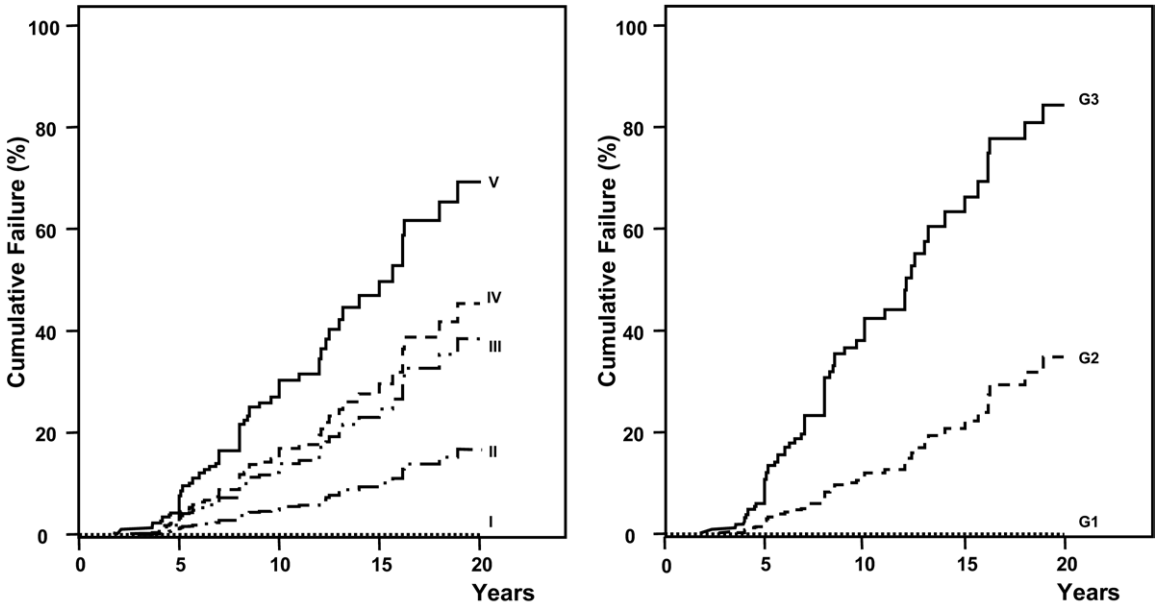


Figure 2. (A) Cox proportional hazard survival curves for end-stage renal disease (ESRD) in the study cohort. Patients were divided in relationship to histological class (grades I to V) according to Lee's classification. Data were adjusted for age, sex, presence of microhematuria at onset, presence of arterial hypertension at renal biopsy, serum creatinine level at renal biopsy, and proteinuria at renal biopsy. (B) Cox proportional hazard survival curves for ESRD in the study cohort. Patients were divided in relationship to histological class (G1 to G3) according to the new classification. Data were adjusted for age, sex, presence of microhematuria at onset, presence of arterial hypertension at renal biopsy, serum creatinine level at renal biopsy, and proteinuria at renal biopsy.

greater baseline serum creatinine level (adjusted HR, 1.50; 95% CI, 1.10 to 2.07; $P = 0.013$) and 1.0 g/24 h greater baseline urinary protein excretion (adjusted HR, 1.28; 95% CI, 1.07 to 1.52; $P = 0.006$).

The simpler histological classification allowed the enrollment of a larger number of patients for each grade of renal lesion and permitted validation of our system on a large homogeneous IgA nephropathy population followed up over a long period in a single center. Univariate and multivariate statistical analysis indicated no overlap between different grades in our classification; however, we did not evaluate whether our new classification was more accurate compared with others reported in the literature.

The identification of clinical and histological factors at renal biopsy that affect disease progression in patients with IgA nephropathy has stimulated abundant research during the past 20 years. Considering the supposed benign nature and slow progression of the disease and relatively aggressive nature of proposed interventions (eg, steroids and other immunosuppressive regimens), it is important to understand which patients might or might not progress and benefit from these therapeutic interventions. Most studies from Europe, Asia, and Australia focused on 5- to 10-year follow-up[20-36] and reported renal survival rates ranged from 74%[32] to 94%[29] at 10 years. A substantially worse prognosis was reported in North American studies, with rates of 57% to 70% at 10 years from onset of disease or biopsy.[16,37-39] Clearly, longer-term follow-up is important considering the very low proportion of events, even after 10 years of observation. However, only 6 studies looked at survival over a longer time frame of 20 years, with rates ranging from 50% to 83%.[21,22,24,25,29,34]

A critical and comparative appraisal of available studies of survival in IgA nephropathy cohorts is difficult for several reasons. First, there are inconsistencies in the definition of the beginning of the observation, which may be at the time of renal biopsy[16,20,28,30,32,33,35-38] or apparent onset of disease.[21-26,29,31,34,39] Second, different end points (including increased serum creatinine level, doubling of serum creatinine level, or ESRD, defined as the need for regular dialysis or renal transplantation) were used in the studies.

Third, statistical analyses used several options, but were simple (typically univariate analysis without adjustment for potential confounders). Fourth, in general, few studies had a follow-up longer than 20 years, and there is extreme variability in histological lesions and renal function in the studied cohorts. Finally, the potential confounding by different diagnostic and therapeutic approaches was not considered in detail in analyses of multicentric databases, proven because studies enrolled cohorts of both treated and untreated patients and analyses did not account for this variable. Taken together, these aspects highlight the potential for misleading results in the presence of significant heterogeneity of disease and management patterns.

Review studies conducted to date by D'Amico[40,41] identified 3 levels of clinical and histological prediction of an adverse outcome in adult patients with IgA nephropathy according to significance by multivariate analysis (so-called "strong predictors"), univariate or multivariate analysis (so-called "moderate predictors"), and univariate analysis only (so-called "poor predictors"). The major contribution of this analysis focused on the importance of histological lesions and highlighted the need for consensus on adequate classification of the disease. Two main types of classification were suggested by Waldo in a special report on IgA nephropathy[42]: the "lumped" system like those of Lee et al,[15] Mina and Murphy,[43] and Haas,[16] and the "split" system like those of Kobayashi et al,[44] Andreoli and Bergstein,[45] Alamartine et al,[29] and Waldo et al.[46] The lumped systems are simple and easily applicable in multicenter studies, but their weakness is the lack of flexible interpretation. The split system gives a more detailed analysis of each lesion of the 4 major compartments (glomeruli, tubules, interstitium, and vessels), thus giving a global score. Although the study of single lesions in a biopsy specimen allows identification of specific markers of damage in comparing 2 or more renal biopsy specimens from the same patient, grading of progressive severity of histological lesions using our new lumped system triggers a good definition of risk progression using statistical analysis. This validation in a large cohort of patients with IgA nephropathy followed up over a long time suggests that this classification may be preferred with respect to that of Lee et al,[15] who enrolled only 20 patients.

Our data are consistent with other data reported in the literature. Conflicting results for degree of hematuria, whether microscopic or macroscopic, lose their prognostic values at multivariate analysis in most studies. To the best of our knowledge, this study represents the largest analysis of survival of patients with IgA nephropathy in which a multivariate approach was adopted (Table 8), with an appropriate model designed to adjust for potential confounders that may have biased previous reports. Our study also was based on a predefined study protocol with all analyses set a priori to avoid the potential for data dredging. Furthermore, we chose ESRD (need for dialysis or transplantation) as our predefined outcome of interest, which is more valid and informative in terms of doubling of serum creatinine level. This latter outcome may be misleading because many patients with IgA nephropathy start with moderate renal function impairment (serum creatinine levels up to 2.3 mg/dL [203.3 μmol/L]) and remain in a steady state for several years.[47]

The study has several limitations. We included in our survival analysis both treated and untreated patients, when, in particular, antihypertensive agents may have a role in retarding the progression of renal disease. Our choice was to not adjust for the potential confounding effect of antihypertensive drugs, particularly angiotensin-converting enzyme inhibitors, which were introduced in the 1990s and might have influenced the natural history of disease. We based our choice on the following considerations. Their use is now considered standard care, and the largest proportion of our patients received this treatment, with no significant differences among histologic grades; and we did not aim to ascertain the role of immunosuppressive and other treatments on the history of disease considering that this is the role of randomized controlled trials, rather than cohort designs.[48,49] Although this is the largest cohort reported to date (n = 437), the single-center nature of the report may affect its external validity. The only study with a similar sample size was that of Koyama et al[34] (n = 448), which included a large proportion of pediatric patients. In that study, only 335 adult patients were evaluated by means of multivariate analysis for risk

Table 8. Renal Survival and Risk Factors at Multivariate Analysis in Most Large Series of Patients With IgA Nephropathy Reported in the Literature

Reference	No. of Patients	Follow-Up (mo)	Starting Observation		Renal Survival From ESRD (%)		Risk Factors at Multivariate Analysis				
			At Onset	At Renal Biopsy	10 y	20 y	Microhematuria	Renal Failure	Proteinuria	Hypertension	Histological Lesions
D'Amico et al,[21] 1986	365	79	Yes		85	66			Yes		Yes
Beukhof et al,[22] 1986	75	92	Yes		84	67	Yes	Yes	Yes	Yes	
	75	64		Yes	75	—					
Bogenschutz et al,[27] 1990	239	59		Yes	80	—		Yes			Yes
Rekola et al,[28] 1990	209	76		Yes	83	—			Yes		
Alamartine et al,[29] 1991	282	96	Yes		94	83			Yes	Yes	Yes
Johnston et al,[30] 1992	220	65		Yes	83	—		Yes			
Katafuchi et al,[32] 1994	225	48		Yes	74	—		Yes	Yes		Yes
Koyama et al,[34] 1997*	448	142	Yes		85	61		Yes	Yes		
Ibels et al,[31] 1994	121	107	Yes		93	—			Yes		Yes
	121	61		Yes	86	—					
Haas et al,[16] 1997	109	ND		Yes	57	—			Yes	Yes	
Radford et al,[37] 1997	148	45		Yes	67	—		Yes			Yes
Bartosik et al,[38] 2001	298	70	Yes		65	—					
	298	57		Yes	62	—			Yes	Yes	
Li et al,[36] 2002	168	89		Yes	82	—		Yes	Yes	Yes	Yes
Current study	437	108		Yes	81	60	Yes	Yes	Yes		Yes

Abbreviation: ND, not done.

*The study of Koyama et al included a proportion of pediatric patients. Only 335 adult patients were included in the multivariate analysis for risk factors.

factors, and there was no subgroup analysis for assessment of this item as a potential effect modifier. In short, we attempted an analysis based on long-term follow-up of 20 years in association with use of multivariate analysis to address the potential limitations of available data. The population of interest was Caucasian, with different genetic characteristics from Asian patients.

In conclusion, IgA nephropathy is characterized by extreme variability in clinical course and slow progression to ESRD in more than 40% of patients in long-term follow-up. Microscopic hematuria, serum creatinine level, daily proteinuria, and severity of histological lesions were associated significantly with adverse outcomes. What is the usefulness of this information in clinical practice and particularly clinical research? Debate exists on the appropriateness of using immunosuppressive regimens in low-risk populations. The use of the new simple histological classification associated with clinical indicators that we identified may be considered for evaluating the risk of progressive renal damage

when making a decision about treatment in clinical settings. Furthermore, inclusion of high-risk populations in randomized controlled trials might enhance the power of these studies because of greater event rates needed for smaller sample sizes.

ACKNOWLEDGMENT

The authors thank Giovanni Pannarale and Loreto Gesualdo for review of renal biopsies and Francesco Pesce and Mariella Mastrolonardo for technical assistance.

REFERENCES

1. D'Amico G: The commonest glomerulonephritis in the world: IgA nephropathy. Q J Med 245:709-727, 1987

2. Julian BA, Waldo FB, Rifai A, Mestecky J: IgA nephropathy, the most common glomerulonephritis worldwide: A neglected disease in the United States? Am J Med 84:129-132, 1988

3. Schena FP: A retrospective analysis of the natural history of primary IgA nephropathy worldwide. Am J Med 89:209-215, 1990

4. Coppo R, Amore A, Hogg R, Emancipator S: Idiopathic nephropathy with IgA deposits. Pediatr Nephrol 15: 139-150, 2000

5. Schena FP, for the Italian Group of Renal Immunopathology: Survey of the Italian Registry of renal biopsies: Frequency of renal diseases for 7 consecutive years. Nephrol Dial Transplant 12:418-426, 1997

6. Espanol de Glomerulonefritis: Evolucion de la frecuencia de las glomerulonefritis primarias y secundarias en Espana en los anos 1991 y 1992. Nefrologia 14:228-296, 1994

7. Smith SM, Tung KS: Incidence of IgA-related nephritides in American Indians in New Mexico. Hum Pathol 16:181-184, 1985

8. Central Committee of the Toronto Glomerulonephritis Registry: Regional program for the study of glomerulonephritis. Can Med J 124:158-161, 1981

9. Research Group on Progressive Chronic Renal Disease: Nationwide and long-term survey of primary glomerulonephritis in Japan as observed in 1850 biopsied cases. Nephron 82:205-213, 1999

10. Manno C, Giancaspro V, Schena FP, e Gruppo di Immunopatologia Renale della Societa' Italiana di Nefrologia: Rapporto finale sul Registro Italiano delle Biopsie Renali (anni 1987-1995). Giorn It Nefrol 15:281-290, 1998

11. Gesualdo L, Di Palma AM, Morrone LF, Strippoli GF, Schena FP, for the Italian Immunopathology Group, Italian Society of Nephrology: The Italian experience of the national registry of renal biopsies. Kidney Int 66:890-894, 2004

12. Wyatt RS, Julian BA, Bachler RW, et al: Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. J Am Soc Nephrol 9:853-858, 1998

13. Simon P, Ramée MP, Autuly V, et al: Epidemiology of primary glomerular disease in a French region. Variations according to period and age. Kidney Int 46:1192-1198, 1994

14. Berger J, Hinglais N: Les dèpots intracapillaires d'IgA-IgG. J Urol Nèphrol 74:694-695, 1968

15. Lee S-MK, Rao VM, Franklin WA, et al: IgA nephropathy: Morphologic predictors of progressive renal disease. Hum Pathol 13:314-322, 1982

16. Haas M. Histologic subclassification of IgA nephropathy: A clinicopathologic study of 244 cases. Am J Kidney Dis 29:829-842, 1997

17. Schena FP, Coppo R: IgA nephropathies, in Davison AM, Cameron JS, Grunfeld JP, et al (eds): Oxford Textbook of Clinical Nephrology (ed 3). New York, NY, Oxford University, 2004, pp 470-501

18. Churg J, Bernstein J, Glassock R. Glomerular Diseases (ed 2). Tokyo, Japan, Igaku-Shoin, 1995

19. Lebacqz K, Levine RJ: Respect for persons and informed consent to participate in research. Clin Res 25:101-107, 1977

20. Nicholls KM, Fairley KF, Dowling JP, Kincaid-Smith P: The clinical course of mesangial IgA associated nephropathy in adults. Q J Med 53:22-50, 1984

21. D'Amico G, Minetti L, Ponticelli G, et al: Prognostic indicators in idiopathic IgA mesangial nephropathy. Q J Med 59:363-378, 1986

22. Beukhof JR, Kardaun O, Schaafsma W, et al: Toward individual prognosis of IgA nephropathy. Kidney Int 29:549-556, 1986

23. Woo KT, Edmondson RPS, Wu AYT, et al: The natural history of IgA nephritis in Singapore. Clin Nephrol 25:15-21, 1986

24. Kusumoto Y, Takebayashi S, Taguchi, T, et al: Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and adult Japanese. Clin Nephrol 28:118-124, 1987

25. Noel LH, Droz D, Gascon M, Berger J. Primary IgA nephropathy: From the first-described cases to the present. Semin Nephrol 7:351-354, 1987

26. Velo M, Lozano L, Egido J, et al: Natural history of IgA nephropathy in patients followed up for more than ten years in Spain. Semin Nephrol 7:346-350, 1987

27. 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 10:137-147, 1990

28. Rekola S, Bergstrand A, Buch H: IgA nephropathy. Development of hypertension in IgA nephropathy as a marker of poor prognosis. Am J Nephrol 10:290-295, 1990

29. Alamartine E, Sabatier JC, Guerin C, et al: Prognostic factors in mesangial IgA glomerulonephritis: An extensive study with univariate and multivariate analyses. Am J Kidney Dis 18:12-19, 1991

30. Johnston PA, Brown JS, Braumholtz DA, Davison AM: 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 304:619-627, 1992

31. Ibels LS, Györy AZ: IgA nephropathy: Analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. Medicine 73:79-102, 1994

32. Katafuchi R, Oh Y, Hori K, et al: An important role of glomerular segmental lesions on progression of IgA nephrop-

athy: A multivariate analysis. Clin Nephrol 41:191-198, 1994

33. Yagame M, Suzuki D, Jinde K, et al: Value of pathological grading in prediction of renal survival in IgA nephropathy. Nephrology 2:107-117, 1996

34. Koyama A, Igarashi M, Kobayashi M, for Members and Coworkers of the Research Group on Progressive Renal Disease: Natural history and risk factors for immunoglobulin A nephropathy in Japan. Am J Kidney Dis 29:526-532, 1997

35. D'Altri C, Manno C, Rossini M, et al: Studio clinicopatologico retrospettivo in 543 pazienti affetti da nefropatia IgA. G Ital Nefrol 4:425-432, 2001

36. Li PK, Ho KK, Szeto CC, et al: Prognostic indicators of IgA nephropathy in the Chinese-clinical and pathological perspectives. Nephrol Dial Transplant 17:64-69, 2002

37. Radford MG, Donadio JV, Bergstralh EJ, Grande JP: Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol 8:199-207, 1997

38. Bartosik LP, Lajoie G, Sugar L, Cattran DC: Predicting IgA nephropathy. Am J Kidney Dis 38:728-735, 2001

39. Wyatt RJ, Julian BA, Bathena DB, et al: IgA nephropathy: Presentation, clinical course, and prognosis in children and adults. Am J Kidney Dis 4:192-200, 1984

40. D'Amico G: Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. Am J Kidney Dis 36:227-237, 2000

41. D'Amico G: Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol 24:179-196, 2004

42. Wyatt RJ, Emancipator SN, Kon V, et al: IgA nephropathy databank: Development of a system for management of renal biopsy acquired data. Am J Kidney Dis 29:817-828, 1997

43. Mina SN, Murphy WM: A comparative study of the clinicopathologic features in children and adults. Am J Clin Pathol 83:669-675, 1985

44. Kobayashi Y, Tateno S, Shigematsu H: IgA nephropathy: Prognostic significance of proteinuria and histological alterations. Nephron 34:146-153, 1983

45. Andreoli SP, Bergstein JM: Treatment of severe IgA nephropathy in children. Pediatr Nephrol 3:248-253, 1989

46. Waldo FB, Wyatt RJ, Kelly DR, Herrera GA, Benefield MR, Kohaut EC: Treatment of IgA nephropathy in children: Efficacy of alternate-day oral prednisone. Pediatr Nephrol 7:529-532, 1993

47. D'Amico G, Ragni A, Gandini E, Fellin G: Typical and atypical natural history of IgA nephropathy in adult patients. Contrib Nephrol 104:6-13, 1993

48. Samuels JA, Strippoli G, Craig JC, Schena FP, Molony DA: Immunosuppressive agents for treating IgA nephropathy. Cochrane Database Syst Rev CD003965, 2003

49. Strippoli G, Manno C, Schena FP: An evidence-based survey of therapeutic options for IgA nephropathy: Assessment and criticism. Am J Kidney Dis 41:1129-1139, 2003