Outcome of Henoch-Schönlein nephropathy in pediatric patients. Prognostic factors

J. Lucas García, O. Álvarez Blanco, M. J. Sanahuja Ibáñez, P. J. Ortega López and I. Zamora Martín

Unidad de Nefrología Pediátrica. H. U. La Fe. Valencia.

Nefrología 2008; 28 **(6)** 627-632

SUMMARY

Objective: *To analyze epidemiological, clinical and laboratory data, renal survival curve and short-term (2 years) and long-term (5 years) prognostic factors in children with nephropathy secondary to Henoch-Schönlein purpura (HSP).*

Materials and methods: *Retrospective analitic cohort study. Clinical records of 100 children diagnosed with HSP at HIU La Fe from 1975-2006 were reviewed. Statistical analysis was by univariate and multivariate analysis.*

Results: *In 67% of cases, nephropathy coincided with onset of the disease and most commonly manifested hematuria with nonnephrotic proteinuria. 35% of patients were biopsied. The most common histology was mesangial proliferation (46%). Clinical stages at diagnosis were stage B: 63%, stage C: 33%; stage D: 4%. Mean follow-up was 5.25 ± 0.76 years. Renal data at 5 years: Clinical stages: stage A: 49%, stage B: 27%, stage C: 0%, and stage D: 5%. Renal transplant: 5%. Renal survival curve (Kaplan-Meier) at 5 years: 95%. Prognostic factors: the univariate analysis showed that the prognostic factors of poor renal prognosis in both the short and long-term were age greater than 8 years, number of purpura relapses greater than 4 and presence of stage VI histology. The multivariate analysis showed that only the number of relapses was a short-term prognostic factor.*

Conclusion: *1) The clinical and laboratory data reviewed were similar to those reported in the literature. 2) The renal survival curve at 5 years was 95%. 3) Age, number of relapses and histology were prognostic factors. 4) The multivariate analysis showed that only the number of relapses was a short-term prognostic factor.*

Key words: *Children. Purpura. Nephropathy. Henoch-Schönlein. Mesangial proliferation.*

RESUMEN

Objetivo: **Analizar los datos epidemiológicos, clínicos y analíticos, así como la curva de supervivencia renal y los factores pronósticos a corto y a largo plazo de niños con nefropatía de Schönlein-Henoch (NSH).**

Material y método: **Estudio clínico de cohorte retrospectivo analítico. Se revisan las historias clínicas de 100 niños diagnosticados de NSH en el HIU La Fe entre 1975 y 2006.**

Resultados: **La manifestación nefrológica más frecuente fue hematuria con proteinuria no nefrótica. El 35% de pacientes fueron biopsiados. La histología más frecuente fue la proliferación mesangial (46%). Los estadios clínicos al diagnóstico fueron Estadio B: 63%, Estadio C: 33%; Estadio D: 4%. Estadios clínicos a los 5 años: Estadio A: 49%, Estadio B: 27%, Estadio C: 0% y Estadio D: 5%. Trasplante renal: 5%. Curva de supervivencia renal (Kaplan Meier) a 5 años: 95%. Factores pronósticos: En el análisis univariante se evidencia que tanto a corto como a largo plazo los factores de mal pronóstico renal fueron la edad superior a 8 años al debut, el número de brotes de púrpura superior a 4 y la presencia de una estadio VI en la histología. El análisis multivariante muestra que a corto plazo únicamente el número de brotes es considerado factor pronóstico.**

Conclusión: **Se pueden considerar como factores pronósticos, tanto a corto como a largo plazo, la edad al inicio de la enfermedad renal, el nº de brotes y la alteración histológica. Sin embargo, en el análisis multivariante únicamente el nº de brotes constituye un factor pronóstico a corto plazo.**

Palabras clave: Niños. Púrpura. Nefropatía. Schönlein-Henoch. Proliferación mesangial.

INTRODUCTION

Henoch-Schönlein purpura is the most common leukocytoclastic vasculitis in children, and is characterized by deposition of IgA immunoglobulins and IgA-containing immune complexes in the small blood vessels of different tissues, causing the symptoms typical of the disease. The etiology and pathogenesis of this disease are currently unknown. Disease incidence is approximately 14/100.000 inhabitants/year,[1,2] and 75% of cases occur in children aged 2 to 11 years.[2]

The most significant clinical findings include non-thrombocytopenic palpable purpura, periarticular edema and swelling, colic abdominal pain and gastrointestinal bleeding, and nephritis. The disease is usually preceded by a non-specific respiratory tract infection.

Renal signs determine long-term prognosis, and their prevalence ranges from 20% and 60% according to the different reports.[3]

Correspondence: *Jesús Lucas García*
Hospital General Castellón
Avda. Hermanos Bou
12003. Castellón. España
jelugar@hotmail.com

The most common clinical sign of Henoch-Schönlein nephropathy (HSN) is isolated microscopic hematuria, often associated to proteinuria.

The presence of renal failure, arterial hypertension, nephrotic proteinuria, and histological findings at the renal biopsy (proportion of glomeruli with crescents) has traditionally represented a poor prognostic factor.[4]

The proportion of patients who develop chronic end-stage renal disease (ESRD) differs depending on patient selection in the different reports. ESRD eventually occurs in 1.6% of patients who only have isolated hematuria or proteinuria, but in 19.5% of those with a nephrotic or nephritic syndrome.[2]

OBJECTIVE

Objectives of this study included: to analyze the epidemiological, clinical, and laboratory data from patients diagnosed of Henoch-Schönlein nephropathy in a third-level hospital; (2) to determine the short- (2 years) and long-term (5 years) prognostic factors; and (3) to estimate the renal survival curve.

MATERIALS AND METHODS

Design

A retrospective, analytical, cohort clinical study.

Patients

A review was made of the clinical histories of 100 patients diagnosed of Henoch-Schönlein nephropathy and monitored by the pediatric nephrology unit of Hospital Universitario La Fe in Valencia from January 1, 1975 to December 31, 2006. Age at disease onset ranged from 1 and 18 years. Patients were diagnosed at our hospital or referred from other centers after diagnosis.

Mean follow-up time was 5.25 ± 0.76 years (range, 0.2-16.4 years). Ninety-three and 81 patients completed two and five years of follow-up respectively.

Methods

Clinical and laboratory controls were conducted at least six months after HSN and every year in low risk cases, whereas in high risk patients control periodicity was individualized based on the severity of the condition.

Clinical data collected at purpura diagnosis included presence or absence of a history of respiratory tract infection, spectrum of clinical signs, and personal and family history of kidney disease. Laboratory tests included plasma levels of immunoglobulins (IgA) and complement fractions C3 and C4. At HSN diagnosis, the following renal signs were recorded: gross or microscopic hematuria, proteinuria and its quantification, plasma creatinine levels and glomerular filtration rate, and blood pressure (BP). These data were collected at each of the follow-up visits.

The number of purpura relapses was also recorded in each patient.

Definition

Diagnostic criteria of Henoch-Schönlein nephropathy meet the 1990 criteria of the American Collage of Rheumatologists (ACR).

Diagnostic criteria for HSN included the presence at any time during its course of any change in urinary sediment, either hematuria or proteinuria, a nephrotic or nephritic syndrome, as well as a decreased glomerular filtration rate, or arterial hypertension based on the percentile for height, age, and sex according to the reference parameters of the Task Force.[5]

At the onset of nephropathy, patients were classified in the different clinical stages using the clinical classification of Meadow et al, as modified by Counahan et al in 1997, shown below:

A: Normal. Normal physical examination, BP, urine analysis, and glomerular filtration rate.

B: Minor urinary abnormalities. Micro/macrohematuria. Non-nephrotic proteinuria.

C: Active kidney disease. Glomerular filtration rate ≥ 60 mL/min/1.73 m^2 or creatinine increase < 25% of the upper limit for age and sex. Associated to nephrotic proteinuria (≥ 40 mg/m^2/h) or AHT.

D: Renal failure. Glomerular filtration rate < 60 mL/min/1.73 m^2 or creatinine increase > 25% of the upper limit for age and sex. Includes ESRD.

Clinical stages are in turn subdivided into two categories designed as low risk (Stage A and B) and high risk (Stage C and D).

These stages were determined at diagnosis and in the short- (2 years) and long-term (5 years).

Indications for renal biopsy were, in agreement with the unit protocol:

a) Acute nephritic syndrome: hematuria, hypertension, oliguria, and renal failure.
a) Established nephrotic syndrome (time period longer than 15 days): proteinuria in the nephrotic range and hypoalbuminemia.
c) Persistent proteinuria: proteinuria in the nephrotic range (> 40 mg/m^2/day) for more than 1 month, moderate proteinuria (20-40 mg/m^2/day) for more than 3 months or significant proteinuria (> 4 mg/m^2/day) for more than 6 months.

The histological classification used was the one based on the International Study of Kidney Disease in Children (ISKDC):

I: Minimal glomerular lesions.

II: Pure mesangial proliferation.

III: Minimal glomerular lesions or mesangial proliferation with crescents/segmental lesions in < 50% glomeruli.

IV: Stage III with crescents/segmental lesions in 50%-75% glomeruli.

V: Stage III with crescents/segmental lesions in > 75% glomeruli.

VI: Membranoproliferative or pseudomesangiocapillary lesions.

Treatment indications and their results are not the purpose of this study.

Statistics

Short- and long-term prognostic factors were established by a non-parametric univariate analysis using the gamma and Somers' D test. In this first analysis, explanatory variables were age at onset of kidney disease, sex, number of purpura episodes, hematuria, proteinuria, BP, glomerular filtration rate, and initial stage, and the variable to be explained was the short- and long-term clinical stage.

These same variables were subsequently evaluated using a multivariate hierarchical loglinear and logit analysis. In this case, the variable to be explained was the short- and long-term clinical stage, that was grouped into two subsets, low-risk stages (Stages A and B) and high-risk stages (Stages C and D).

SPSS for Windows version 12.00 software was used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Epidemiological data

One hundred pediatric patients were studied between 1975 and 2006, 53% males and 47% females (1.1:1). Mean age at purpura onset was 6.95 ± 0.58 years. Mean age at HSN was 7.14 ± 0.57 years. The interval between occurrence of purpura and nephropathy was 0.22 years, ranging from 0 and 6.84 years. Patients were divided into two groups based on the number of purpura relapses: patients with more than 4 relapses (30%) and patients with less than 4 relapses (67%).

Clinical data

Virtually all study patients had the characteristic skin lesions at diagnosis of Henoch-Schönlein purpura. Fifty-seven percent of patients reported gastrointestinal symptoms and 40% joint symptoms, and HSN occurred at the onset of purpura in 67% of patients. Mention should be made of a case of HSN occurring 6.84 years after diagnosis of purpura.

Table I shows the renal signs at HSN diagnosis. The most common renal sign was hematuria, that was microscopic in 57% and gross in 35% of patients. Only 7 patients had no hematuria. Proteinuria was found in 73% of patients, and was associated to hematuria in most of them (67%). Nephrotic proteinuria occurred in 27% of patients, with a mean value of 97.49 mg/m²/h (95% CI, 45.30-149.69), while non-nephrotic proteinuria was found in 46% of patients, with a mean value of 20 mg /m²/h (95% CI, 15.18-24.81). Nephrotic syndrome was present in 8% of patients at diagnosis, and developed in two additional patients over time. A pure nephrotic syndrome occurred in 8% of patients, and the combination of both nephrotic and nephritic syndromes in 3%.

Table I. Renal signs of HSN

Renal sign	Percentage
Isolated hematuria	25%
Isolated proteinuria	5%
Non-nephrotic proteinuria + hematuria	35%
Proteinuria in the nephrotic range	16%
Nephrotic syndrome	8%
Nephritic syndrome	8%
Nephrotic-nephritic syndrome	3%
Renal failure	11%
Arterial hypertension	14%

Renal failure with a mean glomerular filtration rate of 63 mL/min/1.73 m² (95% CI, 48.82-77.40) was seen at disease onset in 11% of patients.

Fourteen percent of patients had BP values above the 95th percentile for age, height, and sex of the Task Force.

Immunoglobulin IgA was increased in 37% of patients, while high complement levels only occurred in 3% of patients.

Clinical stages at diagnosis, 2 years, and 5 years of follow-up are analyzed in Figure 1. A decrease is seen in high-risk clinical stages at 2 and 5 years of follow-up at the expense of an increase in low-risk stages, so that 50% of patients had no disease evidence at 2 and 5 years of follow-up. The proportion of patients with chronic end-stage renal disease at 5 years was 5%.

Histological data

A renal biopsy was performed in 35% of patients according to the previously stated unit criteria. Repeat biopsies were taken in three patients. Figure 2 shows biopsy results.

Prognostic factors

Among the different variables explored in the univariate analysis as probable short- and long-term prognostic factors, only a number of relapses higher than 4, age over 8 years at the onset of nephropathy, and the presence of a membranoproliferative lesion in the biopsy turned out to be poor prognostic factors (table II).

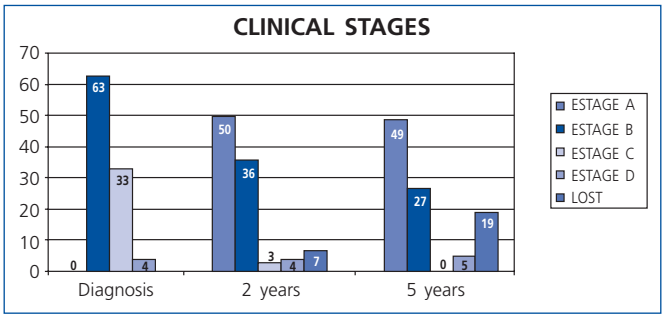


Figure 1. Clinical stages during the follow-up period.

Table II. Statistical significance of variables studied in the short term according to the gamma and Somers' D statistical tests

Variable	p (Gamma)	p (Somers' D)
Age < 8 and > 8	0.039	0.029
Sex: male and female	0.107	0.103
Nephrotic and non-nephrotic proteinuria	0.180	0.165
Microhematuria or macrohematuria	0.836	0.845
Renal failure	0.067	0.063
AHT	0.741	0.742
No. of relapses < 4 and > 4	0.007	0.005
Initial stage	0.654	0.646
Biopsy (Stage I-V and Stage VI)	0.026	0.009

Table II. Statistical significance of variables studied in the long term according to the gamma and Somers' D statistical test

Variable	p (Gamma)	p (Somers' D)
Age < 8 and > 8	0.012	0.01
Sex: male and female	0.382	0,382
Nephrotic and non-nephrotic proteinuria	1	1
Microhematuria or macrohematuria	1	1
Renal failure	0.068	0.021
AHT	0.460	0.460
No. of relapses < 4 and > 4	0.03	0.024
Initial stage	0.364	0.335
Biopsy (Stage I-V and Stage VI)	0.006	0.000

Special mention should be made of the highly significant correlation between the short- and long-term stage seen in our study (p values of 0.000 and 0.000 according to the gamma and Somers' D tests respectively). Thus, the clinical status at 2 years predicted for the status at 5 years of follow-up.

The multivariate study (table III) showed that only the number of relapses remained as a short-term prognostic factor. All other variables showed no short- and long-term statistical significance. The smaller number of patients analyzed long-term may probably have had an influence on the lack of statistical significance in that period.

Kaplan-Meier survival curves

Figure 3 shows the renal survival curve at 5 years of follow-up, considering chronic end-stage renal failure as the final event.

DISCUSSION

The morbidity and mortality of Henoch-Schönlein purpura is dictated by renal involvement by the disease. Henoch-Schönlein nephropathy (HSN) is currently an uncommon cause of chronic end-stage renal disease (ESRD) in children, accounting for 1.2% and 1.7% of patients entering an extrarenal clearance program in the US and Europe respectively.[6,7] According to the 1990 Spanish registry of chronic kidney disease in pediatric patients (REPIR), HSN causes 1.4% of ESRD cases.[8]

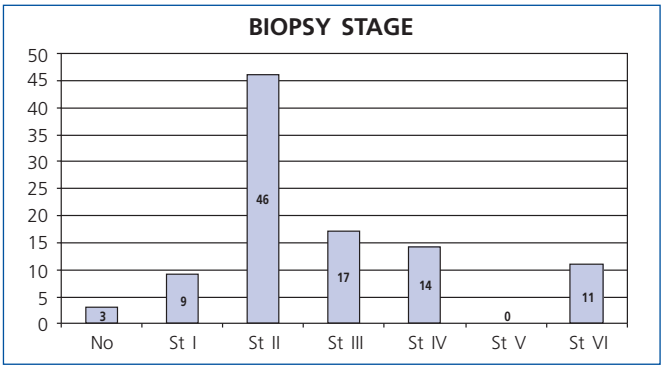


Figure 2. Biopsy stages according to the International Study of Kidney Disease in Children.

There are reports about the prognostic factors of nephropathy giving very disparate results. The purpose of our study was to analyze, in addition to the epidemiological and clinical data on nephropathy, the short- and long-term prognostic factors of the disease, as well as the renal survival curve. The rationale for this study was the few publications available about long-term follow-up of patients with HSN.

In our series, the clinical signs of Henoch-Schönlein purpura were similar to those reported in other publications.[9-11] Our study enrolled patients already diagnosed of HSN, and was therefore not intended to assess its frequency in children with Henoch-Schönlein purpura. In this series, kidney involvement was found at the time of purpura onset in 67% of patients. The nephrological clinical signs were also similar to those previously reported. The most common finding was hematuria (in 93% of patients), whereas associated hematuria and proteinuria were seen in 67% of cases. Nephrotic and nephritic syndromes occurred in 8% of patients, while its combination was only found in 3% of cases. Coppo et al,[12] however, in a study on 219 patients with HSN, reported minimal urinary abnormalities in 47% of cases, nephrotic syndrome in 25%, renal failure in 31%, and hypertension in 23%. Other authors, such as Kawasaki et al,[10] reported a series of cases similar to ours with 15% of nephrotic syndrome, 8% of nephritic syndrome, and 4% of rapidly progressive glomerulonephritis. Vila et al[13] emphasized that hematuria with non-nephrotic proteinuria was the most common finding in a population of 764 patients with Henoch-Schönlein purpura with a 20% incidence of nephropathy.

According to some publications,[2,14] an initial follow-up period of Henoch-Schönlein purpura of at least 6 months is recommended in order to detect urinary abnormalities. In our series, one patient experienced nephropathy 6.84 years after disease onset. This finding leads us to question the follow-up time of these patients, as well as the etiology of their renal involvement.

Clinical stages in our patients did not therefore differ from those reported in other series. The spectrum of clinical signs, and thus the clinical stages at disease onset, are highly influenced by the type of center providing the data (selection bias). The clinical course is also variable depending on the patient group reported, so that while ESRD eventually occurs in 12%-19% of patients in specialized centers, the proportion

Table III. Logit analysis in the short-term study

	Odds ratio	CI (95%) min	CI (95%) max	p
Glomerular filtrarion rate	4,963	0.042	9,883	0.048
No. of relapses	3,013	0.259	5,766	0.032
Proteinuria	3,414	-1,978	8,805	0.215
Hematuria	-2,439	-5,185	0.308	0.082
BP	-0.789	-3,805	2,228	0.608
Sex	-1.1	-3,675	1,476	0.403
Age	0.174	-2,318	2,666	0.891
Initial stage	-3,607	-9,998	2,784	0.269

Logit analysis in the long-term study

	Odds ratio	CI (95%) min	CI (95%) max	p
Glomerular filtration rate	24,148	-10,587	10,635	0.996
No. of relapses	1,877	-0.938	4,691	0.191
Proteinuria	40,527	-14,802	14,883	0.996
Hematuria	-0.157	-2,896	2,583	0.911
BP	1,661	-2,192	5,514	0.398
Sex	-2,176	-6,464	2,112	0.32
Age	-0.401	-3.12	2,318	0.773
Initial stage	-41,469	14,884	14,801	0.996

in non-specialized centers is only 0%-3%.[7] Thus, Chang et al[11] reported a 100% survival curve at 10 years, similar to the 96% reported by Kawasaki et al.[10] Coppo et al[12] and Scharer et al[7] published values of 75% and 73%, respectively. Our study showed a 95% survival curve at 5 years of follow-up.

The most common histological finding in our biopsied patients was mesangial proliferation (ISKDC stage II), with stage distribution being similar to that reported in other series.[10,13] The proportion of crescents and the chronicity index have been considered poor prognostic factors.[4,7,10] There are, however, other publications where biopsy findings did not have statistical significance as poor prognostic factors.[9,12,15] In our patients, the presence of a stage VI (membranopoliferative histological lesion) was found to be a poor prognostic factor, both in the short and long term, in the univariate analysis.

The vast majority of publications on long-term follow-up of HSN studied prognostic factors at the end of follow-up, with a highly variable observation period in each patient. In the Coppo et al[12] series including 219 patients (136 adults and 86 children) with a mean follow-up time of 4.5 years, a Cox multivariate regression analysis suggested age and female sex, as well as persistent proteinuria during follow-up, as prognostic factors.

Sharer et al[7] analyzed the prognostic factors for progression of renal damage in a population of 200 children with Henoch-Schönlein purpura with a 30% incidence of nephropathy, and reported as prognostic factors renal failure at diagnosis, nephrotic syndrome, and the severity of histological changes, defined as the proportion of glomerular crescents. By contrast, age, sex, initial arterial hypertension, and purpura recurrence were not prognostic factors.

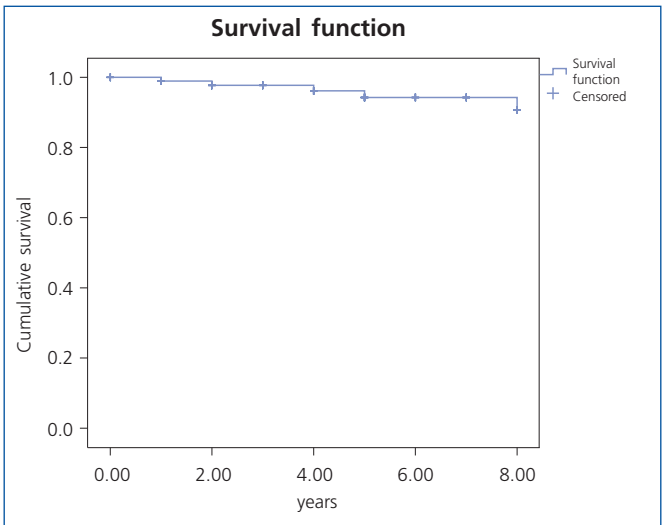
Sevgi Mir et al[9] recently published a study on 114 patients with Henoch-Schönlein purpura with a 58% incidence of nephropathy in which a significant correlation was established between the clinical signs (Stages C and D) at the onset of nephropathy and the short-term (6 months) and long-term (mean, 52 months, with a minimum of 1 year) clinical outcome. Age, sex, glomerular filtration rate, and arterial hypertension had no statistical significance in this study.

In our series, however, the presence of a membranoproliferative lesion at histology, age older than 8 years at onset of nephropathy, and more than 4 relapses were both short- and long-term poor prognostic factors in the univariate analysis. When these variables were analyzed with a multivariate analysis, only the number of relapses continued to be a short-term prognostic factor. Probably, no statistical significance was found for other factors because of sample size.

Prognosis of HSN has traditionally been more unfavorable in adults as compared to children. However, in another study conducted by Coppo et al[15] comparing the clinical course of HSN in adult and pediatric patients requiring a renal biopsy, the authors concluded that the final outcome was similar in both groups, with remission rates of 32% in adults and 31.6% in children, and occurrence of chronic kidney disease in 31.6% and 24.5% of children and adults respectively. No significant differences were seen in the renal survival curve in adults and children at 5 and 10 years. Poor prognostic factors in adults included renal failure, proteinuria higher than 1.5 g/day, and arterial hypertension, while no such prognostic factors were found in children. This study may have a selection bias.

Finally, we would like to emphasize the correlation between the clinical stages at 2 and 5 years (p 0.000), so that the short-term clinical status predicts for the long-term clinical stage with a high degree of reliability. However, as recommended by some authors,[2,16,17] long-term clinical follow-up should be performed, particularly in patients who have required a renal biopsy.

These widely disparate results as regards prognostic factors suggest that Henoch-Schönlein nephropathy is a disease with a very uncertain and variable prognosis. Further multicenter,



	2 years	5 years	8 years
Patients at risk	93	81	24

Figure 3. Kaplan-Meier curves.

collaborative studies recruiting larger patient samples that would allow us for a more potent statistical treatment are required.

CONCLUSION

1) The clinical and epidemiological characteristics are similar to those reported in the literature.

2) The renal survival curve in the reported series greatly depends on the hospital center providing the data; in our study, a value of 95% was found at 5 years of follow-up.

3) In the univariate analysis, poor prognostic factors, both in the short- and long-term, were considered to be age older than 8 years at onset, more than four purpura relapses, and histological stage VI in the renal biopsy. In the multivariate analysis, only the number of relapses was considered to be a short-term prognostic factor.

4) Clinical status at 2 years predicts for clinical status at 5 years. Long-term follow-up is nevertheless recommended.

ACKNOWLEDGEMENT

We thank Héctor Perpiñan Fabuel for statistical data processing.

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