

Factors Predictive of Outcome in Severe Lupus Nephritis

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● In 1992, we published the results of a prospective, controlled trial of aggressive therapy (high-dose prednisone plus oral cyclophosphamide alone or with plasmapheresis) in 86 patients with severe lupus nephritis. During this study, remission (serum creatinine ≤ 1.4 mg/dL [≤ 123 $\mu\text{mol/L}$] and proteinuria ≤ 330 mg/d of protein) in renal disease occurred in 37 patients (43%). To assess the long-term effect of remission on patient and renal survival, we now report the results of our extended follow-up of these patients. After an average of 10 years of follow-up in the 86 patients, patient survival rates at both 5 and 10 years were 95% in the group that had a remission and 69% at 5 years and 60% at 10 years in the no-remission group ($P < 0.001$). Renal survival rates were 94% at both 5 and 10 years in the remission group compared with 46% at 5 years and 31% at 10 years in the no-remission group ($P < 0.0001$). Features predictive of remission included stable renal function after 4 weeks on therapy, category IV lesion, lower chronicity index, white race, lower urine protein excretion level at baseline, and lower baseline serum creatinine level. The features predictive of end-stage renal disease were higher baseline serum creatinine level, presence of anti-Ro antibodies, and failure to attain a remission. Thus, in patients with the most severe forms of lupus nephritis, a remission of clinical renal abnormalities is associated with dramatic improvement in long-term patient and renal survival.

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INDEX WORDS: Systemic lupus erythematosus (SLE); lupus nephritis; remission; end-stage renal disease (ESRD).

THE EFFECTIVENESS of various immunosuppressive therapies in severe lupus nephritis is usually determined by such outcomes as clinical progression of renal disease, end-stage renal disease (ESRD), or death. Recently, however, attention has begun to focus on the value of such positive outcomes as the resolution of clinical renal abnormalities. The term renal remission has been proposed as an indicator of good prognosis.¹⁻³ In 1992, the Lupus Nephritis Collaborative Study Group⁴ published a large, prospective, controlled trial of the treatment of biopsy-proven severe lupus nephritis. The purpose of this study is to report the results of our extended experience in these patients to define those features that appear to determine long-term prognosis in this patient population.

PATIENTS AND METHODS

Patients

The 86 adult patients participating in the prospective controlled trial of plasmapheresis in severe lupus nephritis conducted from April 1981 to December 1988 comprise the study group. In this retrospective study, we extended the mean follow-up to 120 months. Because there were no significant differences between the two treatment groups during the therapeutic trial, patient data are pooled for the purpose of this follow-up study.

Entry criteria, therapeutic and medical management protocols, and results of the initial study have been previously described.^{4,5} In brief, patients were eligible if they were aged 16 years or older; had systemic lupus erythematosus, defined by the American Rheumatism Association⁶; and had biopsy-proven severe lupus nephritis. Patients with a serum creatinine level greater than 6 mg/dL (>528 $\mu\text{mol/L}$), previous plasmapheresis, or pregnancy were excluded from the study.

Entry criteria for the plasmapheresis study⁴ required histological diagnosis of severe lupus nephritis, and the histological diagnosis, determined by The Pathology Reading Committee of the Lupus Nephritis Collaborative Study Group (see Appendix), was used in the present study. An adequate biopsy contained greater than 10 nonsclerotic glomeruli, and the diagnosis of severe lupus nephritis was based on the presence of proliferation and/or necrosis in greater than 50% of the glomeruli with or without concomitant membranous glomerulonephritis.⁴ This pathological rubric comprises three morphologically discrete forms of lupus glomerulonephritis: (1) segmental glomerulonephritis with active and/or necrotizing lesions in greater than 50% of glomeruli (category III, $>50\%$; 24 patients), (2) diffuse glomerulonephritis (category IV⁷; 35 patients), and (3) membranous glomerulonephritis with superimposed severe segmental ($>50\%$ glomerular involvement) or diffuse proliferative glomerulonephritis (category Vc, $>50\%$ or Vd; 26 patients). One patient was not classifiable. The activity index (maximum score of 24

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See Appendix for a list of additional members of the study group.

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points) and chronicity index (maximum score of 12 points) were determined by The Pathology Reading Committee for each biopsy.⁸⁻¹⁰

Clinical, biochemical, and serological information were obtained on patients at baseline and at specified follow-up times during the initial study. The study was terminated March 1986, but patients were formally followed up through December 1988.⁴ Clinical follow-up has now been extended to June 1998. Information on the current clinical status of the patients with respect to death, ESRD, and biochemical results for serum creatinine and urine protein levels were collected.

Laboratory Analysis

Baseline serum creatinine levels, C3 and C4 complement components, anti-double-stranded DNA antibodies (anti-dsDNA), C1q-binding activity, and cryoglobulin concentrations were determined in a central laboratory, as previously described.¹¹ Serum creatinine was measured by Creatinine Analyzer II (Beckman Instruments, Fullerton, CA) with the use of a modified alkaline-picrate method. Serum C3 and C4 were measured by radial immunodiffusion (Calbiochem-Behring, La Jolla, CA), and anti-dsDNA was measured by radioimmunoassay (Amersham, Arlington Heights, IL). Antibodies to Ro, La, nRNP, and Sm were determined by a single investigator (M.R.) using an enzyme-linked immunosorbent assay with affinity purified antibodies, as previously described.^{12,13}

Treatment Protocol

The details of the treatment protocols for this study have been published.^{4,5} All patients initially were administered 60 mg/d of prednisone orally and 2 mg/kg/d of cyclophosphamide orally. Forty patients were randomized to standard therapy plus plasmapheresis three times weekly for 4 weeks in addition to this treatment. After the initial 4 weeks of treatment, patients who improved clinically were administered cyclophosphamide, 1 mg/kg/d, for an additional month, after which it was discontinued. The dose of prednisone was gradually tapered over a 22-week period to 20 mg on alternate days. Patients whose renal symptoms had worsened at 4 weeks (discussed next) were continued on the initial high-dose prednisone and cyclophosphamide for an additional 4 weeks, and patients in the plasmapheresis arm of the study also were administered an additional 12 treatments. Thereafter, renal and extrarenal flares were treated based on other standardized protocols of intensive drug therapy, as previously described.⁵

A brief description of the protocols follows. Minor extrarenal flare was treated with a return to daily prednisone, 30 mg/d, for 2 weeks. Major extrarenal flare was treated with a return to cyclophosphamide, 2 mg/kg/d, for 5 weeks, followed by 1 mg/kg/d for 3 weeks along with daily prednisone, 60 mg/d, for 3 weeks. Mild renal flare was treated with a return to daily prednisone, 30 mg/d, for 2 weeks. Moderate renal flare was treated with a return to daily prednisone, 60 mg/d, for 4 weeks. Patients with severe renal flare were administered another course of treatment with their initial randomized therapy. After the formal study ended, the course of treatment was determined by the individual investigator.

Outcome Variables

The following outcomes were evaluated from the time of entry onto the study: (1) time to remission (serum creatinine ≤ 1.4 mg/dL [≤ 123 $\mu\text{mol/L}$] and proteinuria ≤ 0.33 g/d of protein) within 5 years of entering the study, (2) time to ESRD (defined by serum creatinine ≥ 6 mg/dL [≥ 528 $\mu\text{mol/L}$] or the initiation of renal replacement therapy), and (3) death.

Assessment of renal function was made at 4 weeks. Worsening of renal function was defined by an increase in serum creatinine level of 0.3 mg/dL or greater (≥ 27 $\mu\text{mol/L}$) or doubling of urinary protein to twice baseline. Patients not meeting these criteria were otherwise considered stable.

Lupus flares were defined as follows: (1) minor extrarenal flare, skin rash, mild hemolytic anemia, mild thrombocytopenia, mild serositis, mild myalgias or arthralgias, or fever without infection; (2) major extrarenal flare, failure of mild extrarenal exacerbation to improve after 2 weeks of increased prednisone dose, severe hemolytic anemia (hemoglobin, < 5 g/dL), severe thrombocytopenia (platelets, $< 50,000/\mu\text{L}$), severe pulmonary hemorrhage, central nervous system involvement, vasculitis, uveitis or retinitis, severe serositis, or severe myositis; (3) mild renal flare, reappearance of active urine sediment (red blood cell casts); (4) moderate renal flare, a sudden increase in serum creatinine level of greater than 0.3 mg/dL (> 27 $\mu\text{mol/L}$) or an increase in proteinuria of greater than 1.0 g/d of protein; and (5) severe renal flare, a sudden increase in serum creatinine level of greater than 1 mg/dL (> 88 $\mu\text{mol/L}$).^{4,5}

Statistical Analysis

Comparison of clinical and laboratory characteristics among the groups of patients was performed using Fisher's exact test for categorical data¹⁴ and Wilcoxon's rank-sum test for continuous data.¹⁵ For the analysis of length of time from study entry to ESRD (renal survival) or death (patient survival), product-limit life-table distributions were compared with the log-rank test statistic.¹⁶ A proportional hazards regression model was used to evaluate potential clinical, laboratory, serological, histological, and therapeutic predictors of progression to ESRD and remission.¹⁶ Results are reported as mean \pm SD, and *P* less than 0.05 is considered significant.

RESULTS

Clinical Renal Remission

Clinical remission occurred in 37 of the 86 patients (43%) with severe lupus nephritis during the initial 5 years of the study. The average time to remission was 16 ± 14 months (median, 10.5 months). Baseline features of the 86 patients and comparisons based on remission status are listed in Tables 1 through 3, and features were similar between the two groups with respect to age, sex, and level of proteinuria (Table 1). White patients were more likely to go into renal remission. Patients entering into remission had a lower

Table 1. Baseline Clinical Characteristics

	All	Remission	No Remission	P*
No. of patients	86	37	49	
Age (y)	32 ± 12	30 ± 11	33 ± 13	NS
Women	72	34	38	NS
Race				
White	54	28	26	<0.05
Black	21	6	15	NS
Other	11	3	8	NS
Blood pressure (mm Hg)				
Systolic	142 ± 19	141 ± 15	142 ± 22	NS
Diastolic	88 ± 12	90 ± 13	87 ± 12	NS
Serum creatinine (mg/dL)†	1.9 ± 1.2	1.2 ± 0.5	2.4 ± 1.3	<0.0001
Median (mg/dL)	1.5	1.0	1.9	
Proteinuria (g/d)	6 ± 4	5.5 ± 3.2	6.2 ± 4.4	NS
Median (g/d)	5.5	5.4	5.7	
Treatment				
Standard	46	23	23	NS
Plasmapheresis	40	14	26	

NOTE. Values reported as number or mean ± SD.

Abbreviation: NS, not significant.

*Remission versus no remission.

†To convert serum creatinine from milligrams per deciliter to micromolar, multiply by 88.

initial level of serum creatinine compared with those who did not experience remission (1.2 ± 0.5 mg/dL [106 ± 44 μ mol/L] versus 2.4 ± 1.3 mg/dL [211 ± 114 μ mol/L]; $P < 0.0001$). An initial serum creatinine level of 1.40 mg/dL or less (≤ 123 μ mol/L) was observed in 27 remission patients (73%) compared with only 13 no-remission patients (26%; $P < 0.0001$). The cumulative proportion of patients achieving remission,

based on level of renal function at entry onto the study, is shown in Fig 1. The cumulative remission rate at 5 years was 8% for patients with a serum creatinine level greater than 2.5 mg/dL (>220 μ mol/L), 48% for patients with a creatinine level of 1.41 to 2.50 mg/dL (124 to 220 μ mol/L), and 78% for patients with a creatinine level of 1.40 mg/dL or less (≤ 123 μ mol/L) at baseline.

Table 2. Baseline Serological Characteristics

	All	Remission	No Remission	P*
No. of patients	86	37	49	
dsDNA (mU/L)	289 ± 541	292 ± 555	287 ± 536	NS
>20	83	36	47	NS
C3 (mg/dL)	40 ± 17	40 ± 19	39 ± 17	NS
<80	84	36	48	NS
C4 (mg/dL)	15 ± 12	12 ± 11	17 ± 11	<0.05
<15	54	28	26	<0.05
Cryoglobulin (μ g/mL)	168 ± 263	231 ± 375	121 ± 108	NS
>21	79	32	47	NS
No. of patients with	80	33	47	
Anti-Ro	27	8	19	NS
Anti-La	6	2	4	NS
Anti-nRNP	35	15	20	NS
Anti-Sm	29	13	16	NS

NOTE. Values reported as number or mean ± SD.

Abbreviation: NS, not significant.

*Remission versus no remission.

Table 3. Baseline Histological Features

	All	Remission	No Remission	P*
No. of patients	86	37	49	
Biopsy (category)				
III (>50%)	24	9	15	NS
IV	35	21	14	<0.05
Vc (>50%), Vd	26	7	19	0.06
Unclassified	1		1	NS
Activity index	12.0 ± 4.7	11.8 ± 4.2	12.1 ± 5.0	NS
≥12	42	16	26	NS
Chronicity index	3.4 ± 2.5	2.3 ± 1.8	4.3 ± 2.6	<0.001
≥4	41	10	31	<0.001

NOTE. Values reported as number or mean ± SD.
Abbreviation: NS, not significant.
*Remission versus no remission.

Some histological features were shown to correlate with patient outcomes (Table 3). Patients with diffuse proliferative glomerulonephritis (category IV) lesions were more likely to enter into remission ($P < 0.05$) than those with severe category III, Vc: >50%, or Vd lesions. The activity index and percentage of patients with an activity index of 12 or greater was similar between the two groups. The proportion of patients with a chronicity index of 4 or greater was significantly greater in the no-remission group, suggesting histological evidence of more advanced and irreversible disease.

Survival Outcomes

Follow-up was 120 ± 65 months overall, with follow-up of 146 ± 51 months for the remission group and 100 ± 67 months for the no-remission group ($P < 0.001$; Table 4). An assessment of renal status was made after 4 weeks of treatment. The proportion of patients with worsening renal function was greater in the no-remission group but not statistically significant (20% versus 5%; $P = 0.06$).

The development of lupus flares was assessed. Throughout the study, the occurrence of either minor or major extrarenal flares was not different

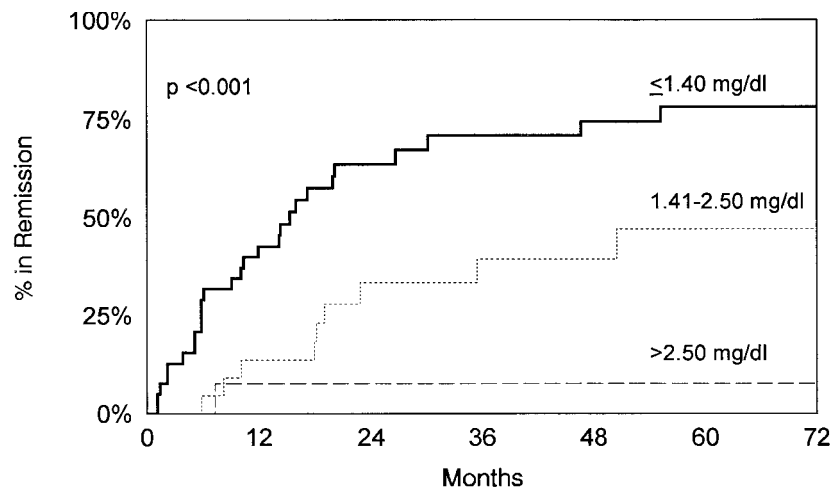


Fig 1. Proportion of patients entering into remission based on serum creatinine level at baseline. At each interval, the number of patients who entered into remission is noted (patients reaching ESRD or death were censored). Serum creatinine level less than 1.4 mg/dL (n = 40), 1.41 to 2.5 mg/dL (n = 27), and greater than 2.5 mg/dL (n = 19).

Month	0	12	24	36	48	60	72
<1.40 mg/dl	0	15	23	25	26	27	27
1.41-2.50 mg/dl	0	3	7	7	8	9	9
>2.50 mg/dl	0	1	1	1	1	1	1

Table 4. Follow-Up

	All	Remission	No Remission	<i>P</i> *
No. of patients	86	37	49	
Follow-up (mo)	120 ± 65	146 ± 51	100 ± 67	<0.001
Median	147	162	117	
Renal status at week 4				0.06
Stable	74	35	39	
Worsening	12	2	10	
Status at last follow-up				
ESRD	22	3	19	<0.01
Renal death	14	1	14	<0.01
Nonrenal death	10	2	7	NS
Stable renal function	40	31	9	<0.0001

NOTE. Values reported as number or mean ± SD.

Abbreviation: NS, not significant.

*Remission versus no remission.

between those patients who experienced remission and those who did not (Fig 2A). Patients not attaining remission, however, were more likely to have renal flares that were often moderate to

severe in nature (Fig 2B). In contrast to these patients, renal flares were uncommon in patients with remission and, when they occurred, were mild to moderate in nature.

The overall patient survival rate at 5 years was 80% and at 10 years was 75% (Fig 3). The overall renal survival rate at 5 years was 68% and at 10 years was 59% (Fig 3). The 5- and 10-year renal survival rates were 50% and 38% in black patients and 74% and 68% in white patients, respectively ($P = 0.01$; figure not shown).

Patient survival rates (Fig 4A) at both 5 and 10 years were 95% in the remission group and 69% at 5 years and 60% at 10 years in the no-remission group ($P < 0.001$). Renal survival rates of 94% at 5 and 10 years (Fig 4B) were also significantly better in the remission group compared with 46% at 5 years and 31% at 10 years in the no-remission group ($P < 0.0001$).

Analysis of renal survival was also evaluated based on histological categorization. Significantly better survival was shown for patients with category IV lesions, with 5- and 10-year survival rates of 79% and 75% compared with 66% and 52% for category III (>50%) and 57% and 47% for category Vc: >50% or Vd lesions, respectively ($P < 0.05$; Fig 4C).

The status of patients at last evaluation is listed in Table 4. Patients not entering into remission were more likely to have progressed to ESRD or had a renal death (on renal replacement therapy at the time of death), whereas the percentage of patients with nonrenal death was similar regardless of whether the patient experienced

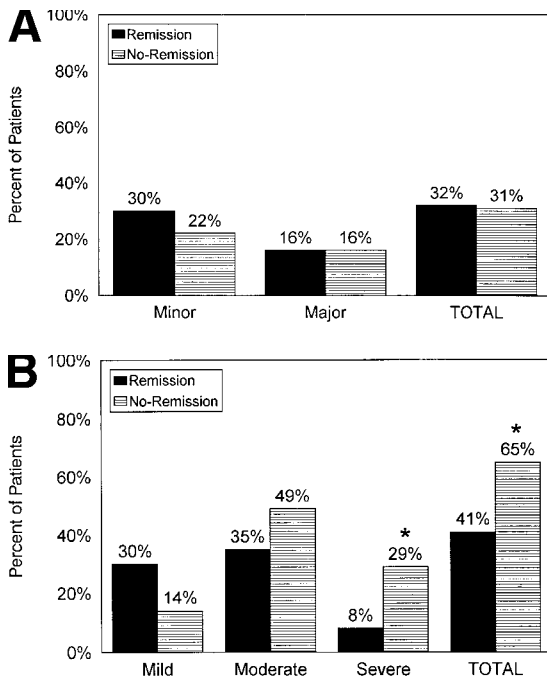


Fig 2. (A) Extrarenal flares in patients with severe lupus nephritis based on remission status. Percentage of patients having a minor or major extrarenal flare (patients could have more than one type of flare) and total number of patients having any extrarenal flare. There were no significant differences between groups. **(B)** Renal flares in patients with severe lupus nephritis based on remission status. Percentage of patients having a mild, moderate, or severe renal flare (patients could have more than one type of flare) and total number of patients having any renal flare. * $P < 0.05$.

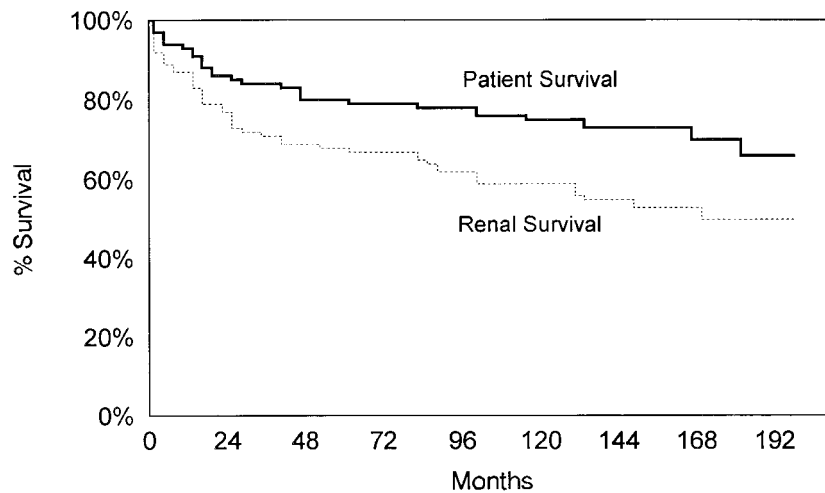


Fig 3. Overall patient and renal survival (censoring for nonrenal death) in patients with severe lupus nephritis. The number of patients at risk in each group is shown under the survival curve.

	Month	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192
Patient Survival		86	81	75	72	67	65	62	61	59	57	54	51	49	35	25	18	5
Renal Survival		86	71	62	56	53	51	48	46	44	42	41	39	38	26	20	14	3

remission. Stable renal function was present in 84% of those patients who entered into remission compared with only 18% in those who did not ($P < 0.0001$). In patients with stable function, serum creatinine level was 0.9 ± 0.3 mg/dL (79 ± 26 μ mol/L) in the remission group and 1.4 ± 0.6 mg/dL (123 ± 53 μ mol/L) in the group that did not have a remission ($P < 0.05$), with 93% of those attaining remission and 67% of those not attaining remission having a serum creatinine level of 1.40 mg/dL or less (≤ 123 μ mol/L). The average level of proteinuria in patients with stable renal function was 0.46 ± 0.6 g/d of protein in the remission group and 0.96 ± 0.7 g/d ($P =$ not significant) in the no-remission group. In the remission group, 58% of the patients with stable renal function continued to have a serum creatinine level of 1.4 mg/dL or less (≤ 123 μ mol/L) and proteinuria of 0.33 g/d or less of protein after 146 ± 51 months of follow-up.

Multivariate Analyses

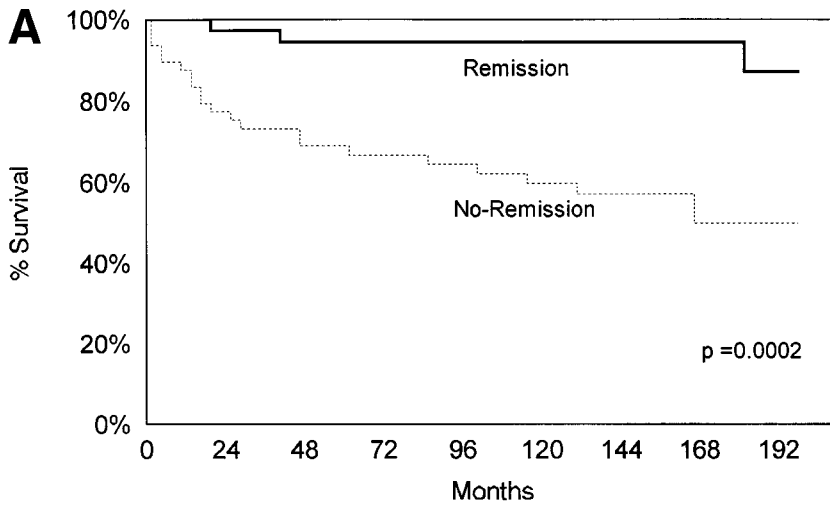
Renal remission status was predictive of ESRD in severe lupus nephritis (Table 5). The risk for progression to ESRD was 8.2 times greater for patients in whom remission did not occur compared with patients with remission. However, for patients entering into remission, the relative risk for progression to ESRD was 0.12 (an 88% risk reduction). Features predictive of remission (Table 6) included renal status at 4 weeks, pres-

ence of category IV lesion (diffuse proliferative glomerulonephritis), chronicity index less than 4, white race, and level of proteinuria or creatinine at baseline.

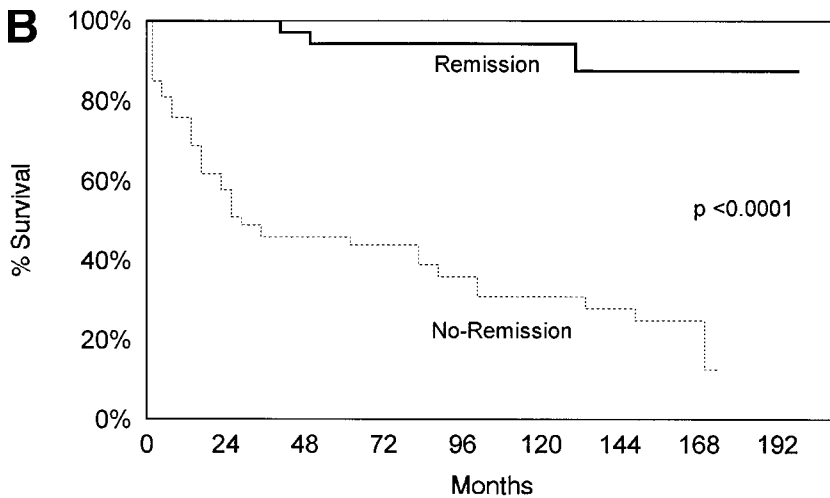
In contrast to those factors predictive of remission, features predictive of ESRD were initial serum creatinine level, presence of anti-Ro antibodies at entry onto the study, and status of remission (Table 5). If remission was left out of the model, initial serum creatinine level (relative risk, 3.0; 95% confidence interval, 2.1 to 4.3; $P = 0.0001$) and presence of anti-Ro antibodies (relative risk, 2.2; 95% confidence interval, 1.1 to 4.4; $P < 0.05$) remained predictive of ESRD, and type of histological lesion became predictive of ESRD, as well. Patients with histological lesions of category III: $>50\%$, Vc: $>50\%$, or Vd had 2.9 times the risk (95% confidence interval, 1.4 to 6.5; $P < 0.01$) for progression to ESRD compared with those patients with category IV lesions (diffuse proliferative glomerulonephritis).

DISCUSSION

Our experience shows that the induction of clinical remission of renal dysfunction is predictive of improved long-term prognosis in patient and renal survival, even for patients with the most severe forms of lupus nephritis. These findings agree with retrospective analyses by Appel et al^{17,18} and Fraenkel et al,² who also found that marked regression or remission of



Month	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192
Remission	37	37	37	36	35	34	32	32	31	31	30	28	28	23	18	14	3
No-Remission	49	44	39	37	33	32	31	30	29	27	25	24	22	13	8	5	3



Month	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192
Remission	37	37	37	36	35	33	31	31	30	30	29	27	27	22	18	14	3
No-Remission	49	34	26	21	19	19	18	16	15	13	13	13	12	5	3		

Fig 4. (A) Patient survival in patients with severe lupus nephritis based on remission status. The number of patients at risk in each group is shown under the survival curve. (B) Renal survival (censoring for nonrenal death) in patients with severe lupus nephritis based on remission status. The number of patients at risk in each group is shown under the survival curve.

clinical renal disease predicted a favorable long-term prognosis in patients with lupus nephritis.

Evidence for the likelihood of renal remission and a favorable long-term outcome appeared early in the course of treatment in our patients. Detailed evaluation after 4 weeks of therapy showed that those patients in whom renal function worsened or failed to improve were significantly less likely to progress to a good outcome. Conceivably, this reflects the early identification of patients in whom the disease process is, for

some innate biological reason, more responsive to the therapy used. Alternatively, those patients in whom the short-term response to therapy is disappointing may have harbored the disease process for a longer period of time, making them intractable to therapy. We are unable to discern between these possibilities on the strength of the current information.

It has previously been reported that serum creatinine level at baseline and histological evidence of advanced renal disease, such as glomeru-

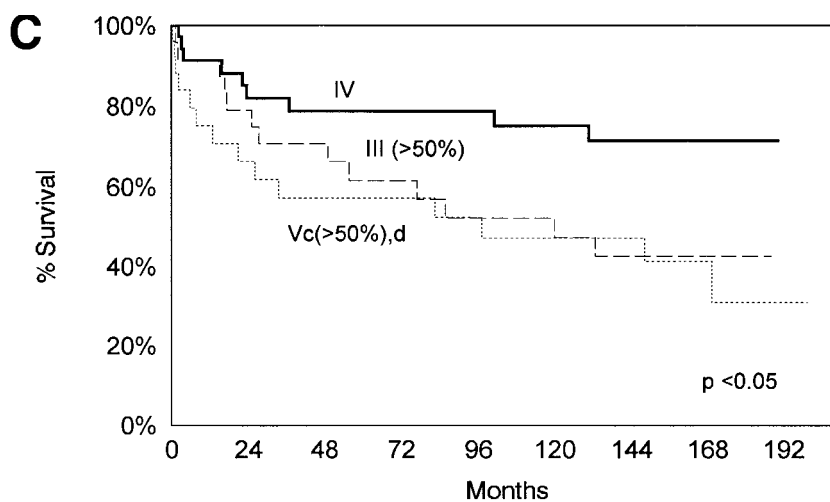


Fig 4. (cont'd) (C) Renal survival (censoring for non-renal death) in patients with severe lupus nephritis based on histological classification. $P < 0.05$ overall; category IV versus III (>50%), $P = 0.05$; category IV versus Vc (>50%), Vd, $P = 0.01$; category III (>50%) versus Vc (>50%), Vd, $P = 0.5$. The number of patients at risk in each group is shown under the survival curve.

Month	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192
IV	35	31	28	27	25	25	23	23	23	22	21	20	20	15	10	7	
III (>50%)	24	23	20	18	17	15	14	13	12	12	12	11	10	7	7	5	
Vc(>50%),d	26	18	16	13	13	13	13	12	11	10	10	10	10	6	5	4	2

lar sclerosis, tubular atrophy, and interstitial fibrosis (ie, high chronicity index), are predictive of progression to ESRD.^{2,3,17,19,20} Baldwin et al²¹ observed that regression or remission of renal disease was achieved in only 17% of the patients with severe lupus nephritis in whom serum creatinine level was greater than 2 mg/dL (176 μ mol/L), but 47% of similar patients with a serum creatinine level less than 2 mg/dL attained a remission. We also found that clinical or histological evidence of advanced (irreversible) renal disease has a significant and negative impact on the likelihood of achieving remission.

The quantity of proteinuria at baseline correlates with the rate of progression to ESRD in diverse disease states associated with nephrotic-range proteinuria.²² Regression or remission of proteinuria in patients with primary glomerular diseases and lupus nephritis has resulted in improved renal survival.^{2,3,17,23} The likelihood of achieving remission and the associated improved renal prognosis is significantly less for patients with greater levels of proteinuria at baseline.

Serological markers for systemic lupus activity, including anti-dsDNA antibodies, complement components C3 and C4, cryoglobulins, and antibodies to Sm, nRNP, or La (SSB), failed to predict clinical outcome. The presence of antibodies to Ro (SSA) was associated with a greater potential for progressing to ESRD. An associa-

tion between antibodies to Ro and severe lupus nephritis has previously been shown.²⁴⁻²⁷ Their presence appears to reflect an underlying immunologic predisposition to the formation of pathogenic immune complexes, which leads to an inflammatory process resulting in progressive glomerular damage and therapeutic unresponsiveness.

The histological category of severe lupus nephritis was highly predictive of the likelihood of attaining remission in our patients. Patients with the lesion of diffuse proliferative glomerulonephritis (category IV) had a greater potential for entering into remission compared with other patients within the category of severe lupus nephritis. The relatively better outcome of patients with diffuse proliferative glomerulonephritis (category IV) was an unexpected result not previously reported. This observation suggests that the acute exudative inflammatory reaction within the glomerulus, although usually dramatic, is often responsive to therapy.

Patient biopsy specimens characterized by severe focal and segmental inflammation and necrosis (category III with >50% involvement) responded less well, suggesting that the underlying pathogenetic mechanism may be less responsive to the therapy used. Focal and segmental histological distribution of the lesions in these latter biopsy specimens suggests a pathogenetic mech-

Table 5. Multivariate Analysis for Predictors of ESRD

Variable	Relative Risk	95% CI	P
Serum creatinine*	2.0	1.4-2.9	0.0001
Anti-Ro present	3.0	1.4-6.4	<0.01
No remission	8.2	2.6-25.6	<0.001

Abbreviation: CI, confidence interval.

*Relative risk per increase of 1 mg/dL.

anism that may be analogous to that responsible for similar lesions in patients with microscopic polyarteritis that may not be mediated by immune aggregates.^{28,29}

Those patients with membranous glomerulonephritis and concomitant severe segmental (category Vc: >50%) or diffuse proliferative (category Vd) lesions had the least tractable course, which may reflect the additive nature of the two distinct pathological patterns to the response to therapy and clinical outcome in these complex patients.

We were able to achieve remission (serum creatinine \leq 1.4 mg/dL and proteinuria \leq 0.33 g/d of protein) in 43% of the patients administered high-dose prednisone and a short course of daily oral cyclophosphamide. Similarly, with combined high-dose steroid therapy and oral cytotoxic agents, Baldwin et al²¹ achieved regression in proteinuria in 50% of the patients with lupus with diffuse proliferative glomerulonephritis. In a recent prospective trial,³⁰ regression (proteinuria, <1 g/d of protein) of clinical renal disease was attained in up to 61% of the patients administered intravenous cyclophosphamide for

a minimum of 30 months. These data appear similar to those in our study.

The importance of maintaining renal remission is evident because patients with flares of lupus nephritis have a poorer prognosis. As in our experience, Moroni et al³¹ observed that lupus nephritis flares occurred far less often in patients maintaining remission compared with patients who relapsed. Furthermore, the relative risk for progressive renal disease (doubling of creatinine level) was 6.8 times greater ($P = 0.03$) for their patients with a flare in renal disease and 27 times greater ($P < 0.00001$) for patients with nephritic flares (defined by increase in creatinine level \geq 30%). Thus, the ability to enter into and maintain remission in severe lupus nephritis appears highly predictive of outcome and must therefore be the goal of therapy.

In conclusion, the occurrence of remission in the course of severe lupus nephritis is associated with significant improvement in long-term patient and renal survival. Based on our observations, remissions are most likely to occur in those patients with better preserved renal function and without histological evidence of irreversible renal damage. Thus, achieving remission of lupus nephritis predicts a more favorable long-term patient and renal survival, and clinicians should make every effort to achieve it. Although not directly examined by our study, it would appear that efforts at early diagnosis and treatment of severe lupus nephritis would optimize the attainment of remission.

APPENDIX

The Lupus Nephritis Collaborative Study Group included the following: *Rush-Presbyterian-St Luke's Medical Center, Chicago, IL*: E.J. Lewis, J.L. Roberts, M.M. Schwartz, R.A. Rodby, H.L. Corwin; *George Washington University, Washington, DC*: J.M. Lachin, S-P. Lan, P. Cleary; *William Beaumont Hospital, Royal Oak, MI*: J. Bernstein, H. Shapiro, B.F. Rosenberg; *Cleveland Clinic, Cleveland, OH*: M.A. Pohl, J. Clough, G. Gephardt; *University of Colorado, Denver, CO*: T. Berl; *Henry Ford Hospital, Detroit, MI*: N. Levin; *University of Iowa, Iowa City, IA*: L.G. Hunsicker, S. Bonsib; *Evanston*

Table 6. Multivariate Analysis for Predictors of Remission

Variable	Relative Risk	95% CI	P
White race	3.9	1.5-10.1	<0.01
Serum creatinine*	0.14	0.06-0.30	0.0001
Proteinuria†	0.74	0.64-0.85	0.0001
Category IV	8.2	3.4-19.8	0.0001
Chronicity index <4	5.6	2.1-14.8	<0.001
Stable at 4 wks	14.0	2.6-74.3	<0.01
No renal flares	2.5	1.2-5.1	<0.05

Abbreviation: CI, confidence interval.

*Relative risk per increase of 1 mg/dL.

†Relative risk per increase of 1 g/d.

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