Clinical Predictors of Recovery and Complications in the Management of Recent-Onset Renal Failure in Lupus Nephritis: A Chinese Experience

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ABSTRACT. ***Objective.*** To investigate the potential clinical predictors associated with the recovery of renal function in recent-onset uremia in patients with lupus nephritis.

Methods. Factors possibly influencing the recovery of renal function in patients with lupus nephritis were examined in a 6 month retrospective cohort study. Records of a sample of 198 consecutive inpatients of recently diagnosed renal failure with lupus nephritis admitted to the University Hospital between 1991 and 2001 were examined. Complete records to assess followup were available for 162 (81.8%). The main outcome factor was recovery of renal function, which was defined as discontinuation of dialysis and over 50% reduction of serum creatinine 3 months after discontinuation of dialysis. Collection of clinical and laboratory data and outcome variables was conducted by 2 separate, blinded groups of clinical specialists with 2 structured abstracting forms.

Results. After 6 months of followup, 96 patients (59.3%) recovered their renal function and 18 (11.1%) had died. After adjustment with Cox proportional hazards models, sex, renal dysfunction duration, renal size, anemia, level of serum phosphate, and intravenous cyclophosphamide (IV CYC) therapy were found to be significantly associated with recovery of renal function. There was significant association between IV CYC therapy and infections. However, in logistic regression analysis, neither CYC therapy nor infections were significantly associated with mortality, and only severe edema and lower serum albumin level were associated with mortality.

Conclusion. Male sex, postponing hospital admission after onset of renal failure, atrophic renal size, and high concentrations of serum phosphate were all predictors of poor recovery of renal function. IV CYC therapy at higher dose had a protective effect on the recovery of renal function. (J Rheumatol 2004;31:701–6)

Key Indexing Terms:
LUPUS NEPHRITIS RENAL FAILURE PREDICTION ANALYSIS
COX PROPORTIONAL HAZARDS REGRESSION

Renal failure is one of the primary causes of death in systemic lupus erythematosus (SLE)[1,2], particularly in the lupus population of low socioeconomic status[3] in developing countries. Renal failure in SLE is often not a true endstage renal disease[4]. Some patients with lupus nephritis may progress slowly to uremia that is usually irreversible, while others may progress rapidly to renal failure that is often reversible with aggressive treatment. However, the acute component of renal function loss in most lupus nephritis cannot be accurately distinguished from chronic injury.

The course of lupus nephritis is usually characterized by relapse and remission. Renal insufficiency frequently appears during the relapse and may recover after cytotoxic therapy. So it is clearly of prognostic importance for clinicians to identify whether the renal failure is reversible or not. Although the US National Institutes of Health (NIH) score is useful in this situation, the renal biopsy is not commonly performed in many developing countries and undeveloped areas. Renal biopsy is also dangerous to some lupus patients in severe relapse. On the other hand, the NIH score is not always useful to the clinician because there is no cut-point to determine when the renal failure becomes irreversible. Therefore, clinical data are also important for the identification of reversibility of renal injury and loss of function. There have been few studies to identify the clinical factors associated with recovery of renal function in these patients.

We conducted a retrospective cohort study to explore the potential clinical predictors associated with the recovery of renal function in patients with recent-onset uremia with lupus nephritis.

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MATERIALS AND METHODS

Study design and patients. A retrospective cohort study was used to gather followup data for patients with recently diagnosed uremia of lupus nephritis who were consecutively admitted to the University Hospital in Guangzhou, China, between 1991 and 2001.

The inclusion criteria were: (1) diagnosis of lupus nephritis according to the American College of Rheumatology 1982[5] revised criteria and proteinuria or cellular casts; (2) uremia requiring dialysis; (3) not more than 3 months since dialysis; and (4) exclusion of prerenal factors (e.g., dehydration or shock), postrenal factors (e.g., kidney stone), and other comorbidities (e.g., diabetic nephropathy or uncontrolled hypertension).

Demographic, clinical, and laboratory data. Study variables and demographic data available from admission and clinic records included: sex, age, duration of SLE, lupus nephritis and renal failure prior to the hospital admission, complications, lupus disease activity, renal size, laboratory examinations, therapeutic options, and infections.

The durations of SLE, lupus nephritis, and renal failure were from diagnosis to admission to hospital. Disease activity was measured with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[6] according to the medical records. Renal size was measured by B-ultrasound scan. In the longest dimension, the normal right kidney is 11 ± 1 cm and the normal left kidney is 11.5 ± 1 cm. Renal size greater than the upper range was defined as swelling and under the lower range as atrophy[7]. Arterial hypertension was defined as supine diastolic blood pressure > 90 mm Hg in 3 consecutive measurements. Edema was divided into 3 grades: slight edema, restricted to ankles and legs; moderate edema, also involving the thighs; and severe edema also involving the pudendum, abdomen, or whole body. Interstitial pulmonary diseases and pleuritis were assessed by chest radiograph. Pericarditis was detected by echocardiography. Features of neuropsychosis included seizures, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, and cerebrovascular accident.

Therapeutic Variables

Cyclophosphamide (CYC). In our hospital, intermittent intravenous (IV) CYC treatment for lupus nephritis had completely replaced oral cyclophosphamide schemes since 1991. However, the interval of therapy and dose were quite different in patients according to the medical records. CYC dose intensity was employed in the study and was divided into 3 grades: none, low dose (average dose < 1.0 g/m^2 body surface area/month), and high dose (average dose ≥ 1.0 g/m^2 body surface area/month).

Corticosteroid. All patients had oral prednisone therapy with the initial dose from 0.5 to 1 mg/kg body weight. IV pulse methylprednisolone was given for 3 consecutive days, with a dose of 1.0 g daily in some patients according to the medical records.

Other medications. The data for any other medications used during the renal recovery induction treatment were also collected and analyzed as study variables. The medications included methotrexate, azathioprine, hydroxychloroquine, nonsteroidal antiinflammatory agents, angiotensin inhibitors, and angiotensin receptor blockers.

Study Outcomes

Short-term reversibility of renal failure. Time zero for the study cohort was the day of admission to hospital. The endpoint of the study was the recovery of renal function, while death and failure to recover renal function 6 months after admission were regarded as censored. The decision to select 6 months of followup for this cohort was based on the experience that patients have little chance of recovery of renal function after 6 months of renal failure. Censoring time for those patients who died was 6 months because their renal function could not recover any more. Recovery of renal function was defined as discontinuation of dialysis and ≥ 50% reduction of serum level of creatinine 3 months after discontinuation of dialysis.

Mortality within 6 months. Mortality during the short-term followup was a second outcome in the study. The study variables of medications and exposures were analyzed for their association with mortality.

Outcomes of longterm followup. Followup continued on the patients who recovered their renal function within 6 months. The second step for the cohort was from discontinuation of dialysis to requirement of dialysis again or to death as the endpoints.

Data Collection

The medical records of all inpatients with an admission diagnosis of uremia of lupus nephritis were identified from computerized hospital admission databases.

First step: The data for study factors and outcomes were blindly collected by 2 separate groups of clinical specialists with 2 abstracting forms, one for study factors and the other for outcomes. There were 2 rheumatologists and one nephrologist in each group. All study variables and most outcome data were obtained from hospital medical records. For a few patients for whom hospital records did not cover 6 months after admission, the outcome data had to be retrieved by contacting patients and then obtaining the records from other hospitals or clinics.

Second step: Further outcomes in patients who recovered their renal function in the first-step followup were collected from hospital medical records or by contacting patients or their families.

Statistical analysis. Cox proportional hazards regression was employed to assess which study factors were significantly related to time to recovery of renal function. The factors associated with death and with infections in the first 6 months were analyzed by logistic regression. The association between IV CYC and infections was tested by Fisher's exact test. Statistical analyses were done using the Stata 6.0 package[8].

RESULTS

Baseline characteristics of the study cohort. From 1567 patients with SLE admitted to hospital during the study period, 198 fulfilled the inclusion criteria and were included in this analysis. Of the 198 patients, 162 (81.8%) had complete followup data. The main cause of loss of followup data was that some patients moved or there was no contact information for them. Some patients moved abroad or to other provinces and could not be reached by telephone or did not respond to 2 mail requests for information. The baseline demographic characteristics of the 36 with incomplete followup data were not significantly different from the 162 with complete data. The baseline characteristics of the 162 available cases are detailed in Table 1.

The total outcomes of the study cohort are given in Table 2.

Short-term followup in the 162 study cases. After short-term followup of 6 months, 96 cases (59.3%) recovered their renal function and 18 cases (11.1%) had died. The time from admission to recovery of renal function ranged from 2 to 20 weeks. Seventy-two percent of the patients who recovered their renal function did so within 3 months of admission to hospital. The time from admission to death ranged from 2 to 28 weeks and 75% within 11 weeks of admission to hospital.

Longterm followup in the 96 cases of renal function recovery. Disease remission induction treatment was continued in a total of 96 cases who recovered their renal function during the short-term followup. The serum creatinine level did not reach normal in 14 of the 96 patients; 10 of these 14 patients needed redialysis at median 17 (range

Table 1. The baseline characteristics of the 162 study subjects.

Female, n (%)	131 (80.9)
Age, yrs, mean ± SD	28.75 ± 12.08
SLE duration, mo, median (IQR)	15 (10, 30)
LN duration, mo, median (IQR)	10 (4, 19)
Renal dysfunction duration, weeks, median (IQR)	4 (3, 9)
Renal size, n (%)	
Normal	63 (38.9)
Atrophy	16 (9.9)
Swelling	83 (51.2)
Hypertension, n (%)	79 (48.8)
Neuropsychosis, n (%)	29 (17.9)
Disease activity (SLEDAI), mean ± SD	21.95 ± 6.31
Urine volume, l/24h, mean ± SD	0.77 ± 0.46
Therapy, n (%)	
IV cyclophosphamide	
No dose	18 (11.1)
Lower dose (< 1.0 g/m^2 per mo)	74 (45.7)
Higher dose (≥ 1.0 g/m^2 per mo)	70 (43.2)
IV pulse methylprednisolone	73 (45.1)

LN: lupus nephritis; IQR: interquartile range.

Table 2. The total outcomes of the study cohort.

Short-term followup in 162 study cases	
No. with renal function recovery (%)	96 (59.3)
Time to renal function recovery after admission, weeks, mean ± SD	9.92 ± 5.01
Median (IQR)	10 (6–13)
No. deaths (%)	18 (11.1)
Longterm followup in 96 cases of renal function recovery	
No. needed redialysis	16 (16.7)
Time to redialysis, months, mean ± SD	27.50 ± 20.87
Median (IQR)	19 (14–45)
No. deaths	8 (8.3)

IQR: interquartile range.

5–45) months after discontinuation of dialysis. Two patients died, one from neuropsychiatric lupus erythematosus, another from cardiac insufficiency. Another 2 cases had been followed for 23 and 31 months, and their serum creatinine levels were 312 and 267 μmol/l. In the 82 patients who reached normal serum creatinine, 6 cases needed redialysis because of severe relapse at median 26 (range 14–64) months after discontinuation of dialysis, 7 cases died from reasons other than endstage renal disease, and another 69 cases remained off dialysis in the period of followup.

Factors associated with recovery of renal function. In a univariate analysis, sex, lupus nephritis duration, renal dysfunction duration, atrophic renal size, severe anemia (hemoglobin < 60 g/l), serum phosphate, serum CO_2, and IV CYC therapy were all significantly associated with recovery of renal function. After adjustment in the Cox proportional hazards regression model only sex, renal dysfunction duration, atrophic renal size, anemia, serum phosphate, and IV CYC therapy remained significantly associated with recovery of renal function. The crude and adjusted hazards ratios for factors associated with recovery of renal function are given in Table 3.

Evaluation of predictive values for each factor associated with recovery of renal function is shown in Table 4. The negative predictive value of non-atrophic renal size was 93.8%. There was little advantage of recovery of renal function in patients with lupus nephritis with atrophic renal size. The negative predictive value of CYC therapy was 88.9%. The high negative predictive value indicated that non-CYC therapy would reduce the possibility of recovery of renal function in patients with the recent onset renal failure of lupus nephritis.

Relationship between intensive therapy and infections. At least one episode of infection was observed in 53 (32.7%) of the 162 subjects in the cohort. In the logistic regression analyses, infection was associated with IV CYC therapy (OR 1.98, 95% CI 1.15–3.39), but was not associated with IV pulse methylprednisolone (OR 1.42, 95% CI 0.74–2.75). The infections occurred in 22.2% (n = 4) of 18 patients with non-CYC therapy, in 24.3% (n = 18) of 74 patients with low dose CYC therapy, and 44.3% (n = 31) of 70 patients with high dose CYC therapy. This tendency to increasing rates of infection was statistically significant by Fisher's exact test ($p = 0.027$). The infections included herpes zoster, pneumonia, urinary infections, septicemia, cryptococcus meningitis, and tuberculosis (Table 5).

Factors associated with mortality in the first 6 months. By logistic regression univariate analysis, only severe edema and serum albumin level were associated with mortality in patients during the 6 month followup period. However, after adjustment with multivariate analysis, serum albumin level did not appear to be associated with mortality. Only severe edema was associated with death (Table 6). Other clinically important factors such as infections, IV CYC therapy, IV pulse methylprednisolone, and other medications, and the demographic, clinical, and laboratory data were not significantly associated with mortality in the univariate and multivariate analyses.

DISCUSSION

This study, in a cohort of consecutive lupus patients with recent-onset renal failure admitted to a university hospital in south China from 1991 to 2001, shows that 59.3% of patients recovered their renal function and 11.1% died within 6 months of admission. Most of the recent-onset renal failure was reversible within 3 months after aggressive therapy for lupus nephritis.

Only a few studies have systematically analyzed the clinical predictors associated with the reversibility of renal function in lupus nephritis with renal failure. Necrotizing and crescentic lupus glomerulonephritis may progress rapidly to renal failure, which is often reversible with effec-

Table 3. Crude and adjusted hazard ratios of variables associated with renal function recovery.

	Crude Hazard Ratio (95% CI)	p	Adjusted Hazard Ratio* (95% CI)	p
Male	0.44 (0.23, 0.82)	0.010	0.51 (0.27, 0.99)	0.048
LN duration, mo	0.986 (0.974, 0.998)	0.026	—	NS
Renal dysfunction duration, week	0.90 (0.85, 0.95)	< 0.001	0.88 (0.83, 0.93)	< 0.001
Renal size				
Atrophy	0.076 (0.010, 0.552)	0.011	0.071 (0.01, 0.53)	0.010
Swelling	1.30 (0.86, 1.97)	0.212	1.23 (0.78, 1.94)	0.380
Anemia				
Slight (Hb ≥ 80 g/l)	0.70 (0.40, 1.23)	0.213	0.65 (0.37, 1.13)	0.128
Moderate (Hb ≥ 60, < 80 g/l)	0.78 (0.46, 1.32)	0.353	0.52 (0.29, 0.92)	0.024
Severe (Hb < 60 g/l)	0.43 (0.22, 0.85)	0.015	0.48 (0.24, 0.95)	0.036
Serum phosphate, mmol/l	0.54 (0.38, 0.79)	0.001	0.53 (0.36, 0.79)	0.002
Serum CO_2	1.07 (1.03, 1.11)	0.001	—	NS
IV cyclophosphamide				
Lower dose (< 1.0 g/m^2 per mo)	6.10 (1.47, 25.23)	0.013	4.11 (0.98, 17.20)	0.053
Higher dose (≥ 1.0 g/m^2 per mo)	13.76 (3.34, 56.60)	< 0.001	11.41 (2.74, 47.53)	0.001

* Adjusted with Cox proportional hazards regression model. LN: lupus nephritis. NS: nonsignificant.

tive immunosuppressive therapy[4]. The duration of renal disease and the rate of change of renal function may indicate the degree to which azotemia is likely to be reversible[9,10]. A short clinical course and rapid deterioration of renal function suggest renal lesions likely to respond favorably to immunosuppressive treatments. The data on "endstage" renal disease with lupus nephritis presented by Coplon, *et al*[11] indicate that patients with asymptomatic lupus have a low probability of discontinuing dialysis, whereas those with active disease of any degree have a significantly greater chance of discontinuing dialysis.

We found that renal size, anemia, serum phosphate, sex, duration of renal insufficiency before hospitalization, and therapies with IV CYC were all significantly associated with the recovery of renal function. The SLE disease activity and the duration of lupus or lupus nephritis were not reliable predictors for the recovery of renal function. The duration of renal insufficiency before hospitalization was an important factor associated with recovery of renal function because patients with severe lupus nephritis usually only have an expectant treatment prior to hospitalization. Intensive treatment with IV CYC or methylprednisolone pulse was initiated after hospitalization.

Renal size was a very important predictor of the reversibility of renal function in the patients with lupus nephritis and renal failure. The hazards ratio of recovery was 0.071 (95% CI 0.01–0.53), which suggested that there was very little opportunity for recovery of renal function in lupus patients with a pair of atrophic kidneys. Possibly this is because the atrophic renal size has resulted from a longterm chronic renal lesion.

Sex was another significant predictor of recovery of renal function. Compared to females, the recovery of renal function in male patients was significantly lower (hazard ratio 0.51, 95% CI 0.27–0.99), and this is consistent with the previously described worse prognosis in men with lupus nephritis compared to women[12]. The duration of renal failure before hospitalization was negatively associated with recovery of renal function (hazard ratio 0.88, 95% CI 0.83–0.93). These results suggest that postponing hospital-

Table 4. Predictive values for each factor associated with recovery of renal function.

	Recovery, n = 96	Nonrecovery, n = 66	Positive Predictive Values, %	Negative Predictive Values, %
Female	85	46	64.9	64.5
Renal failure duration (≤ 4 wk)	66	28	70.2	55.9
Non-atrophic renal size	95	51	65.1	93.8
Hb ≥ 60 g/l	83	48	63.4	58.1
Normal phosphate level	50	17	74.6	51.6
Cyclophosphamide therapy	94	50	65.3	88.9

Table 5. Infection risk of 3 cyclophosphamide therapeutic regimes.

	None, n = 18	Lower Dose, n = 74	Higher Dose, n = 70	p, Fisher Exact Test
Herpes zoster	2	7	13	NS
Pneumonia	3	11	23	0.037
Urinary infections	1	6	12	NS
Septicemia	0	2	5	NS
Cryptococcus meningitis	0	2	4	NS
Tuberculosis	0	2	3	NS
At least one infection	4	18	31	0.027

Table 6. Crude and adjusted OR of variables associated with death.

	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
Slight edema	3.16 (0.31, 31.70)	0.328	2.72 (0.26, 28.33)	0.403
Moderate edema	5.11 (0.59, 44.21)	0.139	3.86 (0.40, 36.79)	0.241
Severe edema	16.84 (1.96, 144.50)	0.010	11.36 (1.11, 116.18)	0.041
Serum albumin, g/l	0.91 (0.84, 0.99)	0.024	0.96 (0.88, 1.05)	0.401

* Adjusted with logistic regression model.

ization by one week could reduce the opportunity to improve renal function by about 12%.

Recent-onset renal failure due to lupus, even if necessitating dialysis, is not synonymous with endstage renal disease. Therefore, the management of these patients is complex. A study by Kimberly and colleagues[13] demonstrated that IV pulse methylprednisolone helped some lupus patients with "endstage" renal disease to discontinue dialysis. However, in our cohort of patients with renal-insufficient lupus nephritis, treatment with IV pulse methylprednisolone was not associated with recovery of renal function. In contrast, IV CYC treatment was significantly associated with recovery of renal function.

The standard therapy of IV pulse CYC for lupus nephritis is a monthly dose of 0.5–1.0 g/m^2 body surface area[14,15]. However, the dose and the pulse interval of CYC used in the study cohort were individually determined based on assessment of severity of disease by each treating physician. In the study cohort, dose intensity of CYC > 1.0 g/m^2 body surface area per month was more effective than a lesser dose. This might indicate that intensive CYC therapy with high dose and/or short interval of pulse could accelerate recovery of renal function. In our experience with treatment of lupus nephritis, the interval of CYC pulse therapy with doses of 0.5 to 0.75 g/m^2 body surface area can sometimes be shortened to 2 weeks for severe lupus nephritis if the leukocyte count is greater than 4.0×10^9/l before each pulse treatment.

Among our patients, therapy with CYC was significantly associated with infections, especially pneumonia. However, we found no association of CYC therapy with death in the logistic regression analysis of mortality risk factors. The variables significantly associated with death were severe edema and low serum albumin concentration.

It is important to identify predictors of reversible renal failure in lupus nephritis because they could offer some guidance to clinicians whether renal function recovery was likely after intensive therapy. However, the renal function prognostic factors in the renal failure of lupus nephritis have been poorly documented. Most studies of the prognosis of lupus nephritis with renal failure have involved patients with endstage renal disease and with renal replacement therapies. There are few reports about prognostic factors concerned with reversible renal failure in lupus nephritis. However, guidelines would be important in the management of lupus nephritis, especially in developing countries where therapeutic issues are very complex in the first few months of renal failure. In some cases, it might be appropriate to continue prednisone, pulse methylprednisolone, and CYC for as long as 3 months after the initiation of dialysis treatments to optimize the chances for recovery of renal function[16]. However, the intensive immunosuppressive therapy might not be beneficial to those patients with few indicators that renal function recovery was likely, especially to the patients with small renal size.

Intensive therapy of patients with lupus is usually much more dangerous in those with renal failure because their disease may be severe and complicated and they have poor overall health status. A clinical decision whether or not to give intensive treatment to these patients may be difficult, because there is little evidence to support which indicators accurately predict benefit from the immunosuppressive treatment. Intensive therapy might benefit a patient with

lupus renal failure with some factors that indicate renal function is reversible, but would accelerate death in those with other or few reversible factors.

The outcome of renal replacement therapy is usually satisfactory for patients in developed countries. The immunosuppressive therapy is potentially risky. Some clinicians may recommend avoiding potentially toxic treatments in patients with lupus nephritis and renal failure, and treatments are focused on preparing patients for transplants. However, the clinical decisions in these settings are quite different in developing countries and especially in undeveloped areas of these countries. Clinicians prefer intensive treatment despite the potential risks, as conservative treatment of recent-onset renal failure often results in death. This is because many patients are unable to meet the cost of lifelong dialysis or the cost of kidney transplant, the only treatment for endstage renal disease.

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