

# The Crescentic Implication of Renal Outcomes in Proliferative Lupus Nephritis

Fanghao Cai, Fei Han, Hongya Wang, Haidongqin Han, Jingyun Le, Lan Lan, Ying Xu, and Jianghua Chen

**ABSTRACT. Objective.** To determine the association between crescents and renal outcomes, and the implications on therapeutic choices.

**Methods.** There were 231 patients with biopsy-proven proliferative lupus nephritis (PLN) who were divided into 4 groups: 59 patients were in the noncrescent group (NC); 59 patients exclusively with segmental crescents were in the segmental crescent group (SC); patients with circumferential crescents were categorized into 2 groups according to the crescentic ratio (C1 had 64 patients with  $\leq 25\%$ , and C2 had 49 patients with  $> 25\%$ ). Their baseline laboratory tests, histopathological manifestations, and outcomes were compared.

**Results.** Remission rates in NC, SC, C1, and C2 groups were 92.1%, 85.4%, 95.0%, and 76.1%, respectively. Fewer patients in the C2 group achieved complete remission than the other 3 groups. For longterm outcomes evaluated by serum creatinine (SCr) doubling or endstage renal disease (ESRD), the renal survival rate was lowest in the C2 group ( $p = 0.003$ ). Including clinical and pathological variables in the Cox proportional hazard regression model separately, the multivariate analysis revealed that these were independent risk factors for SCr doubling or ESRD: baseline SCr (with every 1 mg/dl increase: HR = 1.834, 95% CI 1.465–2.296;  $p < 0.001$ ), hemoglobin (with every 1 g/l increase: HR = 0.970, 95% CI 0.947–0.992;  $p = 0.009$ ), the proportions of cellular crescents (with every 1% increase: HR = 1.040, 95% CI 1.015–1.066;  $p = 0.002$ ) and fibrocellular crescents (with every 1% increase: HR = 1.085, 95% CI 1.013–1.163;  $p = 0.020$ ), and severe renal tubular atrophy (HR = 5.348, 95% CI 1.278–22.373;  $p = 0.022$ ).

**Conclusion.** PLN with crescents  $> 25\%$  had worse renal outcomes both in short and long terms. Proportions of cellular and fibrocellular crescents were independent risk factors for poor renal survival. (First Release February 15 2018; J Rheumatol 2018;45:513–20; doi:10.3899/jrheum.170553)

## Key Indexing Terms:

CRESCENT

LUPUS NEPHRITIS

OUTCOME

Systemic lupus erythematosus (SLE) is an autoimmune disease<sup>1</sup> whose common complication, lupus nephritis (LN), affects 47.7% of patients with SLE in China, reflecting the heterogeneity of SLE<sup>2</sup>. The 2003 International Society of Nephrology and Renal Pathology Society (ISN/RPS) LN classification is the current widely used version. In addition

to the 6 classes, which rely mostly on the percentage of affected glomerular capillary tufts, ISN/RPS recommends explicit pathological reports, although clinical descriptions of various histopathological lesions are lacking<sup>3</sup>. This was probably the reason for controversies in LN classification, especially in the proliferative class<sup>4</sup>. Crescents, the notorious

From the Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University; Key Laboratory of Kidney Disease Prevention and Control Technology, Zhejiang Province; Third Grade Laboratory under the National State Administration of Traditional Chinese Medicine, Hangzhou, China.

Supported by the key research project of precision medicine in National Key Research and Development Plan (2017YFC0907603), Medical Research Funding of Zhejiang Province, China (2013KYA072), and Zhejiang Natural Science Fund (LY15H050004) to Dr. F. Han.

F. Cai, Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University; F. Han, MD, Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University, Key Laboratory of Kidney Disease Prevention and Control Technology, and the Third Grade Laboratory under the National State Administration of Traditional Chinese Medicine; H. Wang, Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University; H. Han, Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University; J. Le, Kidney Disease Center, First Affiliated

Hospital, College of Medicine, Zhejiang University, and Key Laboratory of Kidney Disease Prevention and Control Technology; L. Lan, MD, Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University, Key Laboratory of Kidney Disease Prevention and Control Technology, and the Third Grade Laboratory under the National State Administration of Traditional Chinese Medicine; Y. Xu, MD, Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University, Key Laboratory of Kidney Disease Prevention and Control Technology, and the Third Grade Laboratory under the National State Administration of Traditional Chinese Medicine; J. Chen, MD, Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang University, Key Laboratory of Kidney Disease Prevention and Control Technology, and the Third Grade Laboratory under the National State Administration of Traditional Chinese Medicine.

Address correspondence to Dr. F. Han, 79 Qingchun Road, Hangzhou, Zhejiang Province 310003, China. E-mail: hanf8876@zju.edu.cn

Accepted for publication November 6, 2017.

severe active lesions, are frequent, accounting for about 50% of LN cases<sup>5</sup>. Because crescents manifest at various stages that research has seldom concentrated on, our retrospective cohort study analyzed the clinicopathological features of patients with various crescent formations to examine connections between different types and ranges of crescents and renal outcomes, as well as the therapeutic implications.

## MATERIALS AND METHODS

**Patients.** The clinicopathological archives of 231 adult patients with renal biopsy-proven ISN/RPS class III or class IV, or combined with class V, diagnosed between March 2004 and August 2015 in the Kidney Disease Center of First Affiliated Hospital Zhejiang University were reviewed. The study protocols conformed to the provisions of the Declaration of Helsinki and were approved by the Ethics Committee of our hospital (reference number 201745). All patients fulfilled the 1997 American College of Rheumatology revised criteria of SLE. Patients were then divided into 4 groups according to the crescentic types and proportions. Those without crescent formations were regarded as the noncrescent group (NC; n = 59). The segmental crescents group (SC; n = 59) referred to patients whose pathology exclusively presented segmental crescents. Patients with circumferential crescents were further divided into 2 groups according to the crescentic ratio: crescents  $\leq$  25% (C1; n = 64) and crescents  $>$  25% (C2; n = 49).

**Renal pathology.** One pathologist reported the following pathological features without knowledge of patients' clinical course. Another pathologist reviewed these biopsies and ascertained the percentages of crescents when we did our current study. A crescent is defined as either proliferating extracapillary lesions occupying  $>$  25% of the Bowman's capsular circumference<sup>6</sup>, or  $>$  2-layer cells accumulated in the space. A segmental crescent involves  $<$  50% of the glomerular circumference, while a circumferential crescent takes up more space than that. Circumferential crescents are categorized into cellular, fibrous, and fibrocellular crescents according to their components. Glomerular sclerosis is also calculated as a percentage. In addition, histologic features such as mesangial proliferation, interstitial inflammation, interstitial fibrosis; tubular atrophy, and the immunofluorescence for deposition of immunoglobulin (Ig) M, IgG, IgA, and complement factors C3, C4, and C1q were measured with a semiquantitative scoring system, where 0, 1, 2, and 3 correspond to the degree of severity (absent, mild, moderate, and severe, respectively). Other lesions, such as leukocyte exudation, karyorrhexis/fibrinoid necrosis, thrombosis, tubulitis, and electron-dense deposits were displayed as 0/1 in terms of their existence.

**Clinical evaluation.** Baseline clinical examination included serum anti-dsDNA antibodies, white blood cell count, red blood cell count, platelet count, serum albumin, serum creatinine (SCr), C3, and C4. Urine protein creatinine ratio (uPCR) was tested in substitution of 24-h urine protein.

Treatment response included complete remission, partial remission, and treatment failure<sup>7,8,9,10</sup>. Complete remission requires uPCR  $<$  0.3 g/g, plus normal urinary sediments and serum albumin  $>$  35 g/l, with normal or stable SCr elevated within 25% of the standard upper limit. Partial remission was defined as stable renal function or increased SCr within 25% of previous baseline, plus decreased uPCR at  $>$  50% and  $<$  3.5 g/g, with serum albumin  $>$  30 g/l. Treatment failure was defined as a sustained 25% increase in SCr  $>$  3 months and failure to meet the urinary protein excretion standard for partial remission for longer than 6 months.

The definition of relapse included nephritic relapse and proteinuric relapse<sup>9</sup>. A nephritic relapse indicated a recent increase of SCr by 25% with active urinary sediments. A proteinuric relapse suggests a persistent raise of proteinuria either  $>$  1 g/d after complete remission, or  $>$  2 g/d and twice the previous value after partial remission<sup>10</sup>. Longterm prognosis was evaluated as doubling of SCr or endstage renal disease (ESRD).

**Statistical analysis.** All data were processed by statistical software SPSS

22.0. Quantitative data were expressed as mean  $\pm$  SD, and median (interquartile range). Differences of numerical data with normal distribution were tested by Student t test. Other numerical data and semiquantitative scores were compared by Mann-Whitney U test. Categorical data were interpreted in the form of constituent ratio and percentage, and compared by chi-square test. Cox proportional hazard regression model was applied for multivariate analysis of patients' survival after covariates were screened by univariate analysis. Statistical significance was considered as  $p <$  0.05.

## RESULTS

**Comparisons of baseline clinical and laboratory variables.** The baseline clinical variables of the 4 groups are shown in Table 1. The SC group showed no significant differences in the variables except higher anti-dsDNA-positive percentage compared with NC group. The C1 group showed lower serum albumin level and more acute kidney injury compared with the SC group. The C2 group manifested more severe kidney injuries, specifically the highest proportions of acute kidney injury and nephrotic syndrome, highest SCr level, and lowest serum albumin level. Also, the C2 group showed relatively lower hemoglobin level and higher levels of white blood cells and platelet counts. However, C3 and C4 levels were relatively higher in the C2 group.

**Comparisons of renal histopathological observations.** The renal histopathological variables in 4 groups were shown in Table 2. The proportion of patients with ISN/RPS class IV increased with the group order in the study as they corresponded to crescentic types and ranges. The C2 group had significantly more patients with class IV than the NC group (67.3% vs 47.5%,  $p = 0.03$ ). The percentages of segmental crescents in the SC group were significantly higher than those in the C1 group ( $p = 0.015$ ), while total crescents were lower in the SC group than the C1 group. Both the percentages of segmental crescents and total crescents in C2 group were significantly higher than those in SC and C1 groups.

The groups with crescents were likely to show active injuries such as fibrinoid necrosis, tubulitis, mesangial proliferation, and interstitial filtration, with the first 2 categories showing increasing rates according to group order in the study. The SC group showed a relatively high proportion of subendothelial deposit (no significance). The changes of capillary endothelial cell proliferation and thrombosis in arteriole did not differ significantly among groups. The changes of chronic injury such as proportions of sclerotic glomeruli and interstitial fibrosis did not differ significantly among groups.

The glomerular immunofluorescence intensity of C1q was stronger in the SC group than any other group ( $p = 0.002$  vs NC;  $p = 0.047$  vs C1;  $p = 0.004$  vs C2), whereas the intensity of IgG and IgA was relatively low in the C2 group (no significance).

**Comparisons of treatments and renal outcomes.** The details of treatments and outcomes were listed in Table 3. Relatively higher proportions of the patients in the C2 group received intense treatments such as methylprednisone impulses, intra-

Table 1. Comparison of general information, and baseline clinical and laboratory variables. Values are mean ± SD unless otherwise specified.

Variables	Groups			
	NC	SC	C1	C2
No. patients	59	59	64	49
Sex, m/f	7/52	7/52	6/58	9/40
Age, yrs	36.34 ± 10.60	34.61 ± 12.13	33.97 ± 11.14	36.90 ± 12.69
Hemoglobin, g/l	100.26 ± 20.20	97.59 ± 21.72	97.89 ± 19.39	90.40 ± 16.73 <sup>a,c</sup>
WBC count, 10 <sup>9</sup> /l	4.54 ± 2.32	4.29 ± 1.97	4.76 ± 2.69	5.73 ± 3.05 <sup>b</sup>
Platelet count, 10 <sup>9</sup> /l	141.79 ± 68.67	152.26 ± 76.00	142.57 ± 67.57	169.25 ± 74.69 <sup>c</sup>
Serum albumin, g/l	26.89 ± 6.28	28.90 ± 6.98	26.35 ± 6.65 <sup>b</sup>	24.52 ± 6.15 <sup>b</sup>
uPCR, g/g	4.08 ± 3.00	4.24 ± 2.82	5.54 ± 4.55	6.20 ± 3.42 <sup>a,b</sup>
SCr, mg/dl, median (IQR)	0.88 (0.70–1.32)	0.88 (0.67–1.40)	0.89 (0.72–1.37)	1.32 (0.85–2.27) <sup>a,b,c</sup>
C3, mg/dl, median (IQR)	32.90 (24.30–48.50)	37.15 (24.80–50.35)	37.80 (26.1–48.45)	43.25 (35.08–57.10) <sup>a,c</sup>
C4, mg/dl, median (IQR)	5.60 (4.00–7.20)	6.00 (4.58–8.02)	6.30 (5.00–10.25)	8.30 (5.80–12.00) <sup>a,b</sup>
Anti-dsDNA positive, %	54.4	71.2 <sup>a</sup>	62.9	63.0
Hypertension, %	55.3	47.7	50.0	67.7
Acute kidney injury, %	39.0	32.8	53.2 <sup>b</sup>	68.8 <sup>a,b</sup>
Nephrotic syndrome, %	55.2	46.6	58.1	77.1 <sup>a,b,c</sup>

<sup>a</sup>p < 0.05 compared with NC group. <sup>b</sup>p < 0.05 compared with SC group. <sup>c</sup>p < 0.05 compared with C1 group. WBC: white blood cell; uPCR: urine protein creatinine ratio; SCr: serum creatinine; IQR: interquartile range; C3: complement factor 3; NC: noncrescent group; SC: segmental crescent group.

Table 2. Comparisons of renal pathological data. Values are % or median (IQR) or both unless otherwise specified.

Variables	Groups			
	NC	SC	C1	C2
No. patients	59	59	64	49
ISN/RPS class				
Class III	20.3	15.3	12.5	6.2 <sup>a</sup>
Class IV	47.5	50.8	56.3	67.3 <sup>a</sup>
Class V + III / V + IV	32.2	33.9	31.2	26.5
Crescents, median (IQR), %	0	6.06 (3.57–12.5)	11.44 (7.55–15.19) <sup>b</sup>	37.04 (30.04–62.31) <sup>b,c</sup>
Segmental crescents	0	6.06 (3.57–12.5)	5.13 (2.45–9.30) <sup>b</sup>	21.74; (13.2–27.53) <sup>b,c</sup>
Circumferential crescents	0	0	5.26 (3.23–7.48)	15.63 (6.93–39.17) <sup>c</sup>
Sclerotic glomeruli, median (IQR), %	1.96 (0–10.53)	0 (0–7.43)	1.85 (0–8.99)	4.65 (0–10)
Mesangial proliferation	1 (1–1)	1 (1–1)	1 (1–2)	1 (1–2) <sup>a,b</sup>
Endothelial cells proliferation	78.0	84.5	84.1	81.6
Karyorrhexis/fibrinoid necrosis	1.7	10.2	12.5 <sup>a</sup>	14.3 <sup>a</sup>
Subendothelial deposit	56.3	72.9	67.9	64.3
Tubulitis	18.6	33.9	39.1 <sup>a</sup>	44.9 <sup>a</sup>
Interstitial infiltration	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–2) <sup>a,b,c</sup>
Interstitial fibrosis	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Arteriole thrombosis	3.4	3.4	1.6	2.0
Immunofluorescence of glomerulus				
IgM	2 (1–2)	2 (1–3)	2 (1–2)	2 (1–2)
IgG	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–1)
IgA	2 (1–3)	2 (1–3)	2 (1–3)	2 (0.5–2.5) <sup>b</sup>
C3	3 (2–3)	3 (3–4)	3 (3–3)	3 (3–3)
C4	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)
C1q	2 (1–3)	3 (2–3) <sup>a</sup>	2 (1.75–3) <sup>b</sup>	2 (1–3) <sup>b</sup>

<sup>a</sup>p < 0.05 compared with NC group. <sup>b</sup>p < 0.05 compared with SC group. <sup>c</sup>p < 0.05 compared with C1 group. IQR: interquartile range; ISN/RPS: International Society of Nephrology/Renal Pathology Society; IgM: immunoglobulin M; C3: complement factor 3; NC: noncrescent group; SC: segmental crescent group.

Table 3. Comparisons of therapeutic protocols and outcomes. Values are % unless otherwise specified.

Variables	Groups			
	NC	SC	C1	C2
Followup duration, median (IQR), mos	30.5 (10.6–66.5)	29 (10–52)	29.5 (12–66)	21.5 (8.3–32.25)
Induction treatment				
Methylprednisolone pulse	13	20.4	15.7	35 <sup>a</sup>
Prednisone	23.7	10.2 <sup>a</sup>	17.2	10.2 <sup>a</sup>
Prednisone + IVC	13.6	27.1	29.7 <sup>a</sup>	46.9 <sup>a,b,c</sup>
Prednisone + MMF	40.7	32.2	31.3	20.4
Prednisone + CNI	16.9	20.3	15.6	10.2
Prednisone + MMF + CNI	5.1	10.2	6.2	12.2
Maintenance treatment				
Prednisone	26.2	10.6	19.1	12.9
Prednisone + MMF	45.2	34	34	25.8
Prednisone + CNI	19	21.3	17	12.9
Prednisone + AZA	4.8	6.4	6.4	9.7
Prednisone + MMF + CNI	0	10.6 <sup>a</sup>	6.4	16.1 <sup>a</sup>
Others	4.8	17	17	22.6 <sup>a</sup>
Treatment response				
Complete remission	72.5	54.5	56.7	34.8 <sup>a,b,c</sup>
Partial remission	19.6	30.9	38.3 <sup>a</sup>	41.3 <sup>a</sup>
Treatment failure	7.8	14.5	5.0	23.9 <sup>c</sup>
Longterm prognosis				
Relapse	30.0	24.4	37.5	29.7
Doubling of SCr	8.5	13.6	11.1	28.6 <sup>a,c</sup>
ESRD	6.8	6.8	7.8	18.4

<sup>a</sup>p < 0.05 compared with NC group. <sup>b</sup>p < 0.05 compared with SC group. <sup>c</sup>p < 0.05 compared with C1 group. IVC: intravenous cyclophosphamide; MMF: mycophenolate mofetil; CNI: calcineurin inhibitor; AZA: azathioprine; SCr: serum creatinine; ESRD: endstage renal disease; NC: noncrescent group; SC: segmental crescent group.

venous cyclophosphamide (IVC), and multitarget therapy [the combination of prednisone, mycophenolate mofetil (MMF), and calcineurin inhibitor (CNI)] to induce remission. More patients in the SC group received multitarget therapy during maintenance therapy ( $p = 0.014$ ) compared with the NC group.

Regarding treatment response, the remission rates, including complete remission and partial remission of NC, SC, C1, and C2 groups were, respectively, 92.1%, 85.4%, 95.0%, and 76.1%. The former 3 groups responded similarly to treatment to achieve complete remission, whereas significantly fewer patients in the C2 group achieved complete remission versus the other 3 groups. The treatment failure rate was higher in the C2 group than the C1 group (23.9% vs 5.0%,  $p = 0.005$ ).

Patients with followup for > 6 months were evaluated for longterm prognosis. The median followup durations were similar among patients of NC, SC, and C1 groups, with 30.5, 29, and 29.5 months, respectively. The followup duration of patients in the C2 group was shorter, with a median of 21.5 months. This was attributed to significantly more patients experiencing a doubling of SCr ( $p = 0.003$ , Figure 1) in the C2 group. The relapse rates were comparable in NC, SC, C1, and C2 groups.

*Independent risk factors for renal outcomes.* The independent

longterm prognostic factors with the unfavorable renal outcome as the endpoint, as well as clinical risk factors for doubling of SCr or ESRD, were analyzed in Table 4. Clinical and pathological variables were analyzed separately using a Cox proportional hazard regression model. The multivariate analysis revealed that the following clinical variables were independent risk factors: baseline SCr (with every 1 mg/dl increase: HR = 1.834, 95% CI 1.465–2.296;  $p < 0.001$ ) and hemoglobin (with every 1 g/l increase: HR = 0.970, 95% CI 0.947–0.992;  $p = 0.009$ ). The following pathological characteristics were also independent risk factors: percentages of cellular crescents (with every 1% increase: HR = 1.040, 95% CI 1.015–1.066;  $p = 0.002$ ), fibrocellular crescents (with every 1% increase: HR = 1.085, 95% CI 1.013–1.163;  $p = 0.020$ ), and severe renal tubular atrophy (HR = 5.348, 95% CI 1.278–22.373;  $p = 0.022$ ).

In addition, using the Cox model for analysis of ESRD (Table 5) revealed that the following were independent risk factors: clinical variables, including baseline SCr (with every 1 mg/dl increase: HR = 1.876, 95% CI 1.447–2.433;  $p < 0.001$ ) and uPCR (with every 1 g/g increase: HR = 1.141, 95% CI 1.038–1.253;  $p = 0.006$ ); and pathological characteristics, including glomerular sclerosis (with every 1% increase: HR = 1.040, 95% CI 1.001–1.081;  $p = 0.045$ ), cellular crescents (with every 1% increase: HR = 1.041, 95%

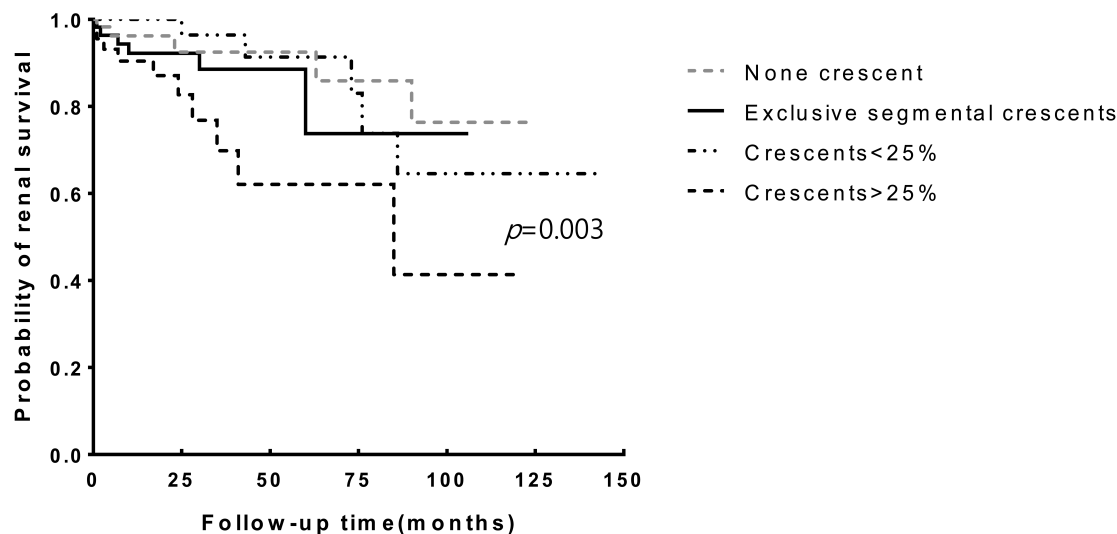


Figure 1. Comparisons of doubling SCr or ESRD long term in patients with different ranges and types of crescents. SCr: serum creatinine; ESRD: endstage renal disease.

CI 1.014–1.070;  $p = 0.003$ ), and fibrocellular crescents (with every 1% increase: HR = 1.104, 95% CI 1.027–1.187;  $p < 0.007$ ).

## DISCUSSION

Crescent formations are common in LN, accounting for 51.5% of patients with LN, according to Zhang, *et al*<sup>5</sup>, and 74.5% of patients with proliferative lupus nephritis (PLN) in our study. Current clinical research on crescents mainly focused on this range. Chen, *et al* divided patients with diffuse PLN into 3 subgroups according to the proportions of crescents, with 10%–24%, 25–49%, and  $\geq 50\%$ <sup>10</sup>, respectively, and found that although patients with crescents  $> 50\%$  presented acute onset and more severe baseline renal manifestations, the prevalence of chronic renal failure was comparable to their counterparts with 10–25% crescents. This probably contributed to their early interference and regular followup. Because the latter subgroup showed longer SLE duration, they seldom presented rapid progressive glomerulonephritis and severe symptoms at the very beginning. Thus, the treatment was always delayed. This indicated the importance of early intensive immunosuppressive therapy, which might improve the renal survival rate of patients with crescents. Zhang, *et al* grouped patients more precisely according to crescentic range<sup>5</sup>. In addition to the correlation of crescentic percentage and unfavorable renal outcomes, their research found that patients mainly with segmental crescents had similar longterm renal outcomes to the patients showing higher proportions of circumferential crescents<sup>5</sup>.

In our study, the clinicopathological characteristics of the C2 group, characterized by  $> 25\%$  crescents, were in accord with previous studies<sup>5,9,10</sup> as having the most serious renal

injury and worst prognosis. Our study selected patients exclusively with segmental crescents and found this group constituted 25.5% of the proliferative patients with LN and 34.4% of patients with crescents. Among all the groups, the SC group showed high frequency of positive serum anti-dsDNA antibody. In histopathology, the SC group showed strong immunofluorescence, especially C1q deposition, which was significantly stronger than in any other group. Renal C1q deposition was associated with serum anti-C1q antibody, which might impede the clearance of apoptotic cells<sup>11</sup>. Prolonged existence of apoptotic cells would trigger or aggravate SLE<sup>1</sup>; this is consistent with the results wherein the SC group had higher frequency of positive serum anti-dsDNA antibody. Moreover, it was reported that the persistence of renal C1q deposition rather than its intensity in the baseline biopsy was associated with poor renal outcome<sup>12</sup>. Therefore, segmental crescents indicated active impairment in both serology and renal pathology. Proper intensive immunosuppressive agents should be prescribed early to prevent further deterioration. In our study, a relatively high proportion of the patients in the SC group were treated with methylprednisone pulses, and prednisone combined with IVC, or with MMF and CNI.

The baseline clinical factors such as high SCr and low hemoglobin were independent risk factors for the unfavorable renal outcome of doubling of SCr or ESRD in our study. Of note, baseline low hemoglobin was a risk factor, possibly because low hemoglobin correlates with SLE activity and the formation of substantial crescents. Another explanation may be attributed to the complication of thrombotic microangiopathy (TMA) that was reported to have poor renal outcomes<sup>13</sup>. Chen, *et al* suggested that patients with crescents

Table 4. Cox hazard analysis of clinical risk factors for doubling of SCr or ESRD in patients with proliferative lupus nephritis.

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
<b>Clinical</b>						
Age	0.983	0.953–1.013	0.265			
Female/male	3.176	1.414–7.131	0.005	1.561	0.494–4.935	0.448
WBC count, 10 <sup>9</sup> /l	1.146	1.018–1.29	0.024	1.034	0.888–1.205	0.665
Hemoglobin, g/l	0.967	0.949–0.985	< 0.001	0.970	0.947–0.992	0.009
Platelet, × 10 <sup>9</sup> /l	0.999	0.994–1.004	0.705			
C3, mg/dl	0.993	0.972–1.014	0.500			
C4, mg/dl	1.035	0.981–1.093	0.204			
Positive anti-dsDNA	0.910	0.459–2.002	0.959			
uPCR, g/g	1.105	1.306–1.178	0.002	1.086	0.989–1.192	0.084
SCr, mg/dl	1.920	1.613–2.285	< 0.001	1.834	1.465–2.296	< 0.001
Albumin, g/l	0.935	0.882–0.992	0.027	0.967	0.899–1.040	0.372
<b>Renal pathological characteristics</b>						
Glomerular sclerosis, %	1.036	1.012–1.061	0.003	1.031	0.998–1.066	0.065
Segmental crescents, %	1.024	1.000–1.048	0.054			
Cellular crescents, %	1.043	1.025–1.060	< 0.001	1.040	1.015–1.066	0.002
Fibrous crescents, %	1.285	1.115–1.482	0.001	0.975	0.785–1.210	0.816
Fibrocellular crescents, %	1.116	1.068–1.166	< 0.001	1.085	1.013–1.163	0.020
Fibrinoid necrosis	0.684	0.163–2.871	0.603			
Mesangial proliferation			0.616			
Mild	0.400	0.052–3.100	0.380			
Moderate	0.452	0.054–3.778	0.464			
Severe	0.672	0.081–5.547	0.712			
Podocyte fusion			0.705			
Localized	1667	0–4.4 × 10 <sup>8</sup>	0.936			
Partial	3455	0–9.2 × 10 <sup>8</sup>	0.930			
Extensive	3423	0–9.1 × 10 <sup>8</sup>	0.930			
Thrombosis	1.290	0.175–9.489	0.803			
Tubulitis	1.568	0.795–3.092	0.194			
Tubular atrophy			< 0.001			
Mild	1.945	0.765–4.949	0.162			
Moderate	7.045	1.339–37.064	0.021	1.200	0.01–15.739	0.890
Severe	10.854	3.482–33.830	< 0.001	5.348	1.278–22.373	0.022
Interstitial infiltration			0.314			
Mild	1.254	0.430–3.660	0.678			
Moderate	1.779	0.501–6.310	0.373			
Severe	5.019	0.899–28.032	0.066			
Interstitial fibrosis			0.102			
Mild	1.380	0.556–3.427	0.487			
Moderate	3.027	0.395–23.218	0.287			
Severe	5.734	1.317–24.963	0.020	0.292	0.045–1.887	0.196
C1q			0.468			
Mild	0.308	0.069–1.382	0.124			
Moderate	0.609	0.198–1.896	0.392			
Severe	0.703	0.228–2.170	0.540			

SCr: serum creatinine; ESRD: endstage renal disease; WBC: white blood cell; C3: complement factor 3; uPCR: urine protein creatinine ratio.

ranging 10%–25% seemed prone to malignant hypertension, and thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome<sup>10</sup>. Therefore, in addition to crescents, particular attention should also be paid to TMA, and treatment should be prescribed promptly once diagnosed.

Regarding renal pathological features, it was severe tubular atrophy, rather than glomerular chronic lesions such as sclerosis or fibrous crescents, that was the independent risk

factor for worse renal outcomes. One reason is that severe tubular atrophy reflects severe glomerular damage and interstitial fibrosis<sup>14,15</sup>. Meanwhile, the probability of constant SLE activity in the tubulointerstitial lesion must be addressed. Yu, *et al* found that tubulointerstitial lesions of some patients were aggravated at the second renal biopsy, although they previously received immunosuppressants such as prednisone, cyclophosphamide, MMF, leflunomide, and azathioprine<sup>14</sup>. Some research has indicated the involvement

Table 5. Cox hazard analysis of clinical risk factors for ESRD in patients with proliferative lupus nephritis.

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	0.979	0.942–1.017	0.276			
Sex, f/m	3.668	1.410–9.545	0.008	1.867	0.541–6.445	0.323
WBC count, × 10 <sup>9</sup> /l	1.252	1.104–1.421	< 0.001	1.104	0.929–1.312	0.261
Hemoglobin, g/l	0.966	0.945–0.988	0.003	0.972	0.943–1.001	0.056
Platelet, × 10 <sup>9</sup> /l	1.003	0.997–1.009	0.705			
C3, mg/dl	0.993	0.968–1.019	0.607			
C4, mg/dl	1.044	0.981–1.112	0.174			
Positive anti-dsDNA	1.364	0.553–3.362	0.5			
uPCR, g/g	1.135	1.060–1.216	< 0.001	1.141	1.038–1.253	0.006
SCr, mg/dl	2.093	1.705–2.569	< 0.001	1.876	1.447–2.433	< 0.001
Albumin, g/l	0.937	0.871–1.008	0.079			
Renal pathological characteristics						
Glomerular sclerosis, %	1.037	1.008–1.067	0.012	1.040	1.001–1.081	0.045
Segmental crescents, %	1.001	0.965–1.039	0.942			
Cellular crescents, %	1.044	1.023–1.064	< 0.001	1.041	1.014–1.070	0.003
Fibrous crescents, %	1.243	1.024–1.509	0.028	0.846	0.617–1.159	0.298
Fibrocellular crescents, %	1.123	1.069–1.180	< 0.001	1.104	1.027–1.187	0.007
Fibrinoid necrosis	0.517	0.069–3.867	0.521			
Mesangial proliferation			0.453			
Mild	0.214	0.026–1.737	0.149			
Moderate	0.346	0.040–3.004	0.336			
Severe	0.262	0.027–2.584	0.251			
Podocyte fusion			0.780			
Localized	1929	0.000–1.1 × 10 <sup>10</sup>	0.948			
Partial	4321	0.000–2.5 × 10 <sup>10</sup>	0.942			
Extensive	3024	0.000–1.7 × 10 <sup>10</sup>	0.945			
Thrombosis	1.874	0.251–14.022	0.541			
Tubulitis	1.816	0.782–4.214	0.165			
Tubular atrophy			0.001			
Mild	1.159	0.393–3.417	0.789			
Moderate	6.746	1.215–37.457	0.029	0.088	7.138–15.739	0.837
Severe	6.326	2.214–31.311	0.002	2.212	0.441–11.106	0.335
Interstitial infiltration			0.643			
Mild	0.993	0.284–3.473	0.991			
Moderate	1.925	0.459–8.065	0.370			
Severe	0.000	0.00–0.00	0.979			
Interstitial fibrosis	0.772	0.248–2.402	0.655			
C1q			0.778			
Mild	0.388	0.054–2.756	0.344			
Moderate	0.765	0.162–3.609	0.735			
Severe	0.813	0.174–3.803	0.792			

ESRD: endstage renal disease; WBC: white blood cell; C3: complement factor 3; uPCR: urine protein creatinine ratio; SCr: serum creatinine.

of Toll-like receptors in the interstice injury in LN<sup>16,17,18</sup>, and it is hard to say whether the aforementioned agents were sufficient. For acute pathological lesions, fibrocellular crescents had higher HR than cellular crescents for longterm renal outcomes. The former sometimes resulted from severe obstruction of Bowman's capsules and subsequent fibroblast infiltration<sup>19</sup>. Sustained profibrotic process irresponsive to current immunosuppressive treatment should also be considered and requires further study.

The risk factors for ESRD were all associated with glomerular injury, including uPCR and SCr of clinical variables, as well as glomerular sclerosis, cellular crescents,

and fibrocellular crescents of pathological index. It was interesting that fibrocellular crescents again had higher HR than cellular crescents. Further research is required to ascertain whether fibrocellular crescents reflect active profibrotic process in the glomeruli and to determine the underlying reasons.

PLN with segmental crescents showed both serological and pathological activity and should receive appropriate intense therapy. PLN with crescents > 25% had worse renal outcomes both in the short and long terms. Proportions of cellular crescents and fibrocellular crescents were independent risk factors for poor renal survival.

## REFERENCES

1. Lorenz G, Desai J, Anders HJ. Lupus nephritis: update on mechanisms of systemic autoimmunity and kidney immunopathology. *Curr Opin Nephrol Hypertens* 2014;23:211-7.
2. Li M, Zhang W, Leng X, Li Z, Ye Z, Li C, et al. Chinese SLE Treatment and Research group (CSTAR) registry: I. Major clinical characteristics of Chinese patients with systemic lupus erythematosus. *Lupus* 2013;22:1192-9.
3. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;15:241-50.
4. Schwartz MM, Korbet SM, Lewis EJ; Collaborative Study Group. The prognosis and pathogenesis of severe lupus glomerulonephritis. *Nephrol Dial Transplant* 2008;23:1298-306.
5. Zhang W, Yuan M, Hong L, Zhou Q, Chen W, Yang S, et al. Clinical outcomes of lupus nephritis patients with different proportions of crescents. *Lupus* 2016;25:1532-41.
6. Austin HA 3rd, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. *Kidney Int* 1984;25:689-95.
7. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;353:2219-28.
8. Wang J, Hu W, Xie H, Zhang H, Chen H, Zeng C, et al. Induction therapies for class IV lupus nephritis with non-inflammatory necrotizing vasculopathy: mycophenolate mofetil or intravenous cyclophosphamide. *Lupus* 2007;16:707-12.
9. Yu F, Tan Y, Liu G, Wang SX, Zou WZ, Zhao MH. Clinicopathological characteristics and outcomes of patients with crescentic lupus nephritis. *Kidney Int* 2009;76:307-17.
10. Chen S, Tang Z, Zhang Y, Liu Z, Zhang H, Hu W, et al. Significance of histological crescent formation in patients with diffuse proliferative lupus nephritis. *Am J Nephrol* 2013;38:445-52.
11. Tan Y, Song D, Wu LH, Yu F, Zhao MH. Serum levels and renal deposition of C1q complement component and its antibodies reflect disease activity of lupus nephritis. *BMC Nephrol* 2013;14:63.
12. Alsuwaida A, Husain S, Al Ghonaim M, Aloudah N, Ullah A, Kfoury H. Prognostic significance of C1q deposition in serial biopsies for predicating the long-term outcome in patients with proliferative lupus nephritis. *Saudi J Kidney Dis Transpl* 2016;27:305-11.
13. Wu LH, Yu F, Tan Y, Qu Z, Chen MH, Wang SX, et al. Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions. *Kidney Int* 2013;83:715-23.
14. Yu F, Wu LH, Tan Y, Li LH, Wang CL, Wang WK, et al. Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. *Kidney Int* 2010;77:820-9.
15. Hill GS, Delahousse M, Nochy D, Tomkiewicz E, Remy P, Mignon F, et al. A new morphologic index for the evaluation of renal biopsies in lupus nephritis. *Kidney Int* 2000;58:1160-73.
16. Anders HJ, Banas B, Schlondorff D. Signaling danger: toll-like receptors and their potential roles in kidney disease. *J Am Soc Nephrol* 2004;15:854-67.
17. Anders HJ, Vielhauer V, Eis V, Linde Y, Kretzler M, Perez de Lema G, et al. Activation of toll-like receptor-9 induces progression of renal disease in MRL-Fas(lpr) mice. *FASEB J* 2004;18:534-6.
18. Benigni A, Caroli C, Longaretti L, Gagliardini E, Zoja C, Galbusera M, et al. Involvement of renal tubular Toll-like receptor 9 in the development of tubulointerstitial injury in systemic lupus. *Arthritis Rheum* 2007;56:1569-78.
19. Shankland SJ, Smeets B, Pippin JW, Moeller MJ. The emergence of the glomerular parietal epithelial cell. *Nat Rev Nephrol* 2014;10:158-73.