Improvement of Outcomes in Patients with Lupus Nephritis: Management Evolution in Chinese Patients from 1994 to 2010

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ABSTRACT. ***Objective.*** To assess how the longterm outcomes have changed over the past decades in Chinese patients with lupus nephritis (LN). The trends in patient manifestation at presentation, treatment pattern, and therapeutic effects were evaluated.

Methods. A cohort of biopsy-proven patients with LN (n = 1945) from January 1994 to December 2010 was analyzed. Treatment regimens, treatment response, renal relapse, and renal outcome were compared at different time periods (1994–1998, 1999–2004, and 2005–2010).

Results. Patients in the later periods had shorter duration of disease, lower serum creatinine value and chronicity at biopsy, and more frequent followup. They were more likely to receive standard-of-care therapies, which included cyclophosphamide, mycophenolate mofetil, and combination therapy. Patients in the later periods had higher probabilities of achieving remission ($p < 0.001$) and lower probabilities of experiencing renal flare ($p = 0.007$). The 5-year renal survival rates were 92.6%, 90.6%, and 94.3% in 1994–1998, 1999–2004, and 2005–2010, respectively. The 5-year risk of endstage renal disease (ESRD) did not differ between 1994–1998 and 1999–2004, but was significantly lower in 2005–2010 (HR 0.40, 95% CI 0.19–0.85 vs 1999–2004). In multivariable Cox analysis, standard therapy was independently associated with lower risk of ESRD (adjusted HR 0.72, 95% CI 0.52–0.98, $p = 0.04$). Variables of renal damage at biopsy (renal function, activity index, and chronicity index) were independently associated with poor outcome.

Conclusion. The outcomes of Chinese patients with LN have improved from 1994 to 2010. With the increased use of standard therapies, the remission rates have increased and renal relapse has decreased.
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Key Indexing Terms:
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Lupus nephritis (LN) affects over half of patients with systemic lupus erythematosus (SLE) and worsens the effects of that disease[1]. Up to 25% of patients with LN will progress to endstage renal disease (ESRD) within 10 years after their diagnosis[2,3,4,5]. The presence of renal damage, particularly ESRD, is associated with a 9-fold increase in mortality compared with SLE patients without renal disease[6].

The outcomes of LN mainly depend on the degree of response to treatment; thus, tremendous efforts have been made to develop effective treatment over recent years[7]. A number of regimens have been assessed in clinical trials such as cyclophosphamide (CYC)[8], mycophenolate mofetil (MMF)[9], calcineurin inhibitors (CNI)[10,11], combination therapy (combining corticosteroids, MMF, and tacrolimus)[12,13], and biologic agents[14,15]. In addition to the efficacious therapies, the severity of renal damage at diagnosis can also influence the treatment response and prognosis. An increased serum creatinine level and chronic lesions at presentation are important predictors for poor outcomes in LN[16]. Therefore, early diagnosis and prompt intervention

with effective therapies is an important way to improve the outcomes of LN.

In addition, healthcare policies and healthcare access play substantial roles in outcomes of LN[17]. It was reported that socioeconomic factors such as limited access to specialized healthcare and lack of health insurance can also result in poor prognosis[18]. China has undergone a rapid economic and sociocultural change involving improvements to the health system during the past 20 years. Medical care and outcomes may have also changed greatly among patients with LN in China.

The main purpose of our study was to investigate how the longterm outcomes of LN have changed during the 17 years from 1994 to 2010. Trends in patient manifestation and renal damage at diagnosis, treatment regimens, treatment response, relapse of disease, and followup frequency were evaluated using data from the Nanjing Glomerulonephritis Registry from 1994 to 2010. We tried to quantify the effect on outcome of the change of treatment modalities in clinical practice, and we examined the independent association between standard therapies and renal outcome.

MATERIALS AND METHODS

Study population. This study evaluated patients with LN in the Nanjing Glomerulonephritis Registry at the National Clinical Research Center of Kidney Diseases, Jinling Hospital, from January 1994 to December 2010. All patients with LN diagnosed through a renal biopsy at the center were included in the registry. Patients were included in our study if they fulfilled the 1997 American College of Rheumatology criteria for SLE and were older than 14 years of age, with biopsy-proven LN. In total, 2276 patients with biopsy-proven LN were reviewed. Patients were excluded if they were 14 years or younger (n = 173), had incomplete inpatient and outpatient records (n = 20), or had a followup duration < 12 months without ESRD (n = 138). That left 1945 patients in the final analysis. This retrospective study was approved by the Ethics Committee of Jinling Hospital (approval number: 2016NZKYKS-005-02).

Main baseline variables. The time of LN diagnosed by renal biopsy was considered as a starting point. Changes in patient characteristics were examined, including demographic characteristics (age, sex), medical history (duration of SLE and LN, prior treatment with immunosuppressive agents, prior dialysis, prior renal biopsy), clinical severity [hypertension, anemia, hypoalbuminemia, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), urinary protein, urine sediment red blood cell (RBC) count, serum creatinine, estimated glomerular filtration rate (eGFR), uric acid, serum C3, serum C4, anti-dsDNA], and pathological characteristics [pathologic classification, activity index (AI), chronicity index (CI)]. The specimens were reviewed by the same pathologist according to the 2003 International Society of Nephrology/Renal Pathology Society classifications[19]. The SLEDAI score was calculated according to the SLEDAI-2K index. The term "duration of LN" means the time from first detection of proteinuria until the institution of renal biopsy, and the term "duration of SLE" means the time from first appearance of SLE symptoms until renal biopsy.

Followup information including clinical variables and important laboratory tests were monitored and recorded at every visit. Data were collected by trained physicians accustomed to standardized case report forms.

Outcomes. Our study focused on changes over time in medical practice, treatment response, renal relapse, and renal survival. Medical care practices included immunosuppressive agents [CYC, MMF, CNI, combined therapy, azathioprine (AZA), leflunomide (LEF), *Tripterygium wilfordii* (TW)] and nonimmunosuppressive therapies [angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB)]. Details of the standard induction therapy protocol for LN in our center are available in Supplementary Data 1 (available from the authors on request). The primary endpoint of the study was ESRD, which was defined as eGFR < 15 ml/min/1.73 m^2 for at least 3 months, or the need for maintenance dialysis or kidney transplant. We assessed the treatment response (complete remission) after induction therapy. Complete remission was defined as a 24-h urinary protein ≤ 0.4 g/day, the absence of active urine sediments, serum albumin ≥ 35 g/l, and normal serum creatinine levels. Partial remission was defined as a ≥ 50% reduction in proteinuria and urinary protein < 3.5 g/day, serum albumin level ≥ 30g/l, and normal or ≤ 25% increase in serum creatinine level from baseline. A modified version of the definition and classification of renal relapse in the 2012 KDIGO Clinical Practice Guideline for LN was adopted for this analysis[20].

Statistical analysis. Patients were stratified into 3 temporal groups based on the time of the biopsy diagnosis: 1994–1998, 1999–2004, and 2005–2010. Trends in characteristics, treatments, and outcomes were assessed. Data were summarized as frequencies and percentages for categorical variables. Continuous variables are presented as median with interquartile ranges (IQR). Categorical variables among groups were compared with the chi-square test or Fisher's exact test, and continuous variables with the Kruskal-Wallis test.

Survival curves were analyzed using the Kaplan-Meier method and were compared using the log-rank test. Kaplan-Meier estimates of the probability of remission, renal relapse, and the renal survival rate were calculated. Renal survival curves found that the proportional hazards assumption was violated, so the extended Cox regression model with time-dependent covariates was used to derive the HR for ESRD between different calendar periods. The calendar periods (CP) variable and its product with time (CP × t) were chosen as the time-dependent variables. Results were adjusted for patient demographics (age, sex) and clinical characteristics at diagnosis (duration of LN, serum creatinine, histological classification, AI, and CI). We also examined the independent association between standard therapy and renal outcome using a multivariable Cox model. All statistical tests were 2-tailed, and p values ≤ 0.05 were significant. Analyses were performed using SAS software version 9.2 and SPSS software version 19.0.

RESULTS

Patient characteristics trends. In this analysis, 1945 biopsy-proven LN patients were included (182 in 1994–1998, 584 in 1999–2004, 1179 in 2005–2010). The median followup duration was 81.7 months (IQR 55.2–116.0).

Table 1 shows the patient characteristics at biopsy based on different time periods. Patients were older, more often had a history of renal biopsy, and had a shorter duration of SLE and LN in the later periods. Patients in the earlier period were more likely to present with hypoalbuminemia and had higher serum creatinine concentration. Patients in later periods had higher levels of SLEDAI score, proteinuria, and urine RBC, and a lower level of serum C4. The rate of low eGFR (< 30 ml/min/1.73 m^2) decreased significantly across the 3 study periods, while the rate of presence of nephrotic-range proteinuria increased. Patients in 1999–2004 had a higher uric acid level, a lower serum C3 level, and a lower rate of positive anti-dsDNA. The sex, previous treatment with immunosuppressive agents, history of dialysis, and anemia rate did not significantly change from 1994 to 2010. The median followup frequency increased from 1.6 (IQR 1.1–2.4)

Table 1. Manifestations of patients with LN at the time of renal biopsy.

Variables	1994–1998, n = 182	1999–2004, n = 584	2005–2010, n = 1179	p
Demographics				
Age at biopsy, yrs	29.4 (24.8–34.7)	30.6 (24.4–36.6)	31.8 (23.5–39.5)	< 0.001
Women	157 (86.3)	514 (88.0)	1018 (86.3)	0.60
Medical history				
Duration of SLE, mos	26.1 (7.2–66.0)	19.3 (5.2–59.5)	20.1 (4.0–61.7)	0.03
Duration of LN, mos	7.53 (3.2–25.0)	6.1 (2.0–25.2)	4.9 (1.6–25.9)	0.01
Previous treatment with immunosuppressive agents	149 (81.9)	447 (76.5)	872 (74.0)	0.08
Prior renal biopsy	3 (1.6)	34 (5.8)	155 (13.1)	< 0.001
Prior dialysis	0 (0.0)	6 (1.0)	26 (2.2)	0.06
Clinical severity				
SLEDAI	10.0 (7.0–13.0)	12.0 (8.0–14.0)	12.0 (10.0–16.0)	< 0.001
Hypertension[a]	83 (45.6)	215 (36.8)	426 (36.1)	0.05
Anemia[b]	152 (83.5)	468 (80.1)	921 (78.1)	0.20
Hypoalbuminemia[c]	120 (65.9)	347 (59.4)	648 (55.0)	0.01
Serum creatinine, mg/dl	0.99 (0.83–1.43)	0.88 (0.71–1.17)	0.75 (0.59–1.07)	< 0.001
eGFR, ml/min/1.73 m^2 [d]				
≥ 90	71 (39.0)	301 (51.5)	756 (64.1)	< 0.001
60–89	54 (29.7)	156 (26.7)	201 (17.0)	< 0.001
30–59	34 (18.7)	78 (13.4)	148 (12.6)	0.08
< 30	23 (12.6)	49 (8.4)	74 (6.3)	0.006
Urinary protein, g/day	1.94 (1.18–2.96)	2.58 (1.24–5.15)	2.39 (1.20–4.37)	< 0.001
< 0.4	6 (3.3)	31 (5.3)	58 (4.9)	0.54
0.4–3.49	144 (79.1)	326 (55.8)	708 (60.1)	< 0.001
≥ 3.5	32 (17.6)	226 (38.7)	413 (35.0)	< 0.001
Urine RBC, × 10^4/ml	22.5 (4.0–160.0)	41.0 (4.0–181.0)	47.0 (5.0–186.5)	0.04
Uric acid, μmol/l	384 (310–489)	394 (317–498)	378 (301–470)	0.04
Serum C3, g/l	0.56 (0.38–0.87)	0.46 (0.35–0.66)	0.50 (0.38–0.69)	< 0.001
Serum C4, g/l	0.25 (0.13–0.40)	0.11 (0.07–0.16)	0.10 (0.06–0.15)	< 0.001
Anti-dsDNA–positive	92 (50.5)	248 (42.5)	626 (53.1)	< 0.001
Pathologic features				
Pathologic classification				
Class II	12 (6.6)	48 (8.2)	58 (4.9)	0.02
Class III/III+V	37 (20.3)	151 (25.9)	314 (26.6)	0.20
Class IV/IV+V	115 (63.2)	308 (52.7)	621 (52.7)	0.03
Class V	18 (9.9)	77 (13.2)	186 (15.8)	0.06
Pathologic AI	8.0 (3.0–11.0)	6.0 (2.0–10.0)	7.0 (2.0–11.0)	0.05
Pathologic CI	2.0 (1.0–4.0)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	0.05
High AI (≥ 12)	38 (20.9)	100 (17.1)	233 (19.8)	0.34
High CI (≥ 4)	49 (26.9)	108 (18.5)	217 (18.4)	0.02
Followup frequency, visits/year	1.6 (1.1–2.4)	2.4 (1.7–3.2)	3.3 (2.5–4.4)	< 0.001

Values are n (%) or median (interquartile range). [a] Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. [b] Anemia was defined as hemoglobin < 120 g/l (women) or < 130 g/l (men). [c] Hypoalbuminemia was defined as serum albumin < 30g/l. [d] The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation: $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female), where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1. SI conversion factors: to convert SCr to μmol/l, multiply values by 88.4. LN: lupus nephritis; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; eGFR: estimated glomerular filtration rate; RBC: red blood cells; AI: activity index; CI: chronicity index; SCr: serum creatinine.

visits per year in 1994–1998 to 3.3 (IQR 2.5–4.4) visits per year in 2005–2010.

The trends in renal pathologic features of these patients are also shown in Table 1. The rate of class IV/IV + V LN decreased across the time periods. Patients in 1999–2004 had a higher rate of Class II LN. There was no significant difference in the rates of class III/III + V LN, Class V LN, high AI (AI ≥ 12), and the median AI/CI. The rate of high CI (CI ≥ 4) was higher in the earlier period.

Treatment regimen trends. After the exclusion of 37 patients whose induction therapy information was unavailable, 1908 patients were included in the analysis of trends in treatment modalities and treatment response.

After the introduction of MMF in 1997 and combination therapy in 2005 (Supplementary Figure 1, available from the authors on request), the proportion of patients who received CYC increased from 25.1% in 1994–1998 to 30.2% in 1999–2004, and then decreased to 21.9% in 2005–2010

(Table 2). The use of MMF increased from 10.6% in 1994–1998 to 20.9% in 2005–2010 (p = 0.005). Also, the use of combination therapy increased from 0% to 22.2% (p < 0.001). Meanwhile, the use of CNI decreased from 12.3% to 4.1% (p < 0.001). The rates of TW combined with corticosteroids decreased from 44.7% to 21.1% (p < 0.001). The number of patients who received AZA or LEF was small (17 patients received AZA and 60 received LEF). The use of ACEI/ARB increased significantly across the study periods (p < 0.001; Table 2). Patients with proliferative LN had similar trends in treatment modalities (Supplementary Table 1, available from the authors on request). In Class II and Class V LN, corticosteroids with TW were the most commonly used therapy (Supplementary Tables 2 and 3, available from the authors on request).

Remission rate changes. Figure 1 shows that patients in later periods had higher Kaplan-Meier estimated complete remission rates (p < 0.001). The percentages of patients who achieved complete remission were 37.4% (67/179), 62.1% (354/570), and 72.9% (845/1159) for the periods of 1994–1998, 1999–2004, and 2005–2010, respectively (p < 0.001). The cumulative probabilities of complete remission at 6 months for the 3 periods were 10.3% (95% CI 6.6–15.8%), 18.7% (95% CI 15.7–22.1%), and 25.1% (95% CI 22.7–27.7%), respectively (Figure 1). Compared with 1994–1998, patients in 1999–2004 and 2005–2010 were also more likely to achieve complete remission (adjusted HR were 2.05, 95% CI 1.57–2.67, and 2.92, 95% CI 2.26–3.76; Supplementary Table 4, available from the authors on request).

Relapse rate changes. For the analysis of renal flare, 1643 patients who achieved overall remission (partial remission or complete remission) were included. As shown in Figure 2A, patients in the later time periods were less likely to have renal relapse (p = 0.007). The risks of renal flare decreased across the time periods, though there was no significant difference between 1994–1998 and 1999–2004 (compared with 1994–1998, adjusted HR were 0.88, 95% CI 0.67-1.16 in 1999–2004, and 0.72, 95% CI 0.55–0.95 in 2005–2010; Supplementary Table 5, available from the authors on request).

Renal survival rate changes. Among the 1945 study participants, ESRD developed in 20.3% (37/182) of patients in 1994–1998, 14.6% (85/584) in 1999–2004, and 6.4% (76/1179) in 2005–2010. The 5-year renal survival rates were 92.6% (95% CI 87.4–95.8%), 90.6% (95% CI 87.8–92.8%), and 94.3% (95% CI 92.7–95.5%) for the periods of 1994–1998, 1999–2004, and 2005–2010, respectively (1994–1998 vs 1999–2004, p = 0.52; 1994–1998 vs 2005–2010, p = 0.009; 1999–2004 vs 2005–2010, p = 0.007; Figure 2B).

There was no significant difference in the risk of ESRD between 1994–1998 and 1999–2004, but the HR of ESRD in 2005–2010 appeared to be significantly lower than in 1999–2004. After 5 years of followup, the adjusted HR for ESRD was 0.76 (95% CI 0.32–1.85) in 1994–1998 (vs 1999–2004) and 0.40 (95% CI 0.19–0.85) in 2005–2010 (vs 1999–2004). The risks of ESRD after 10 years of observation did not significantly differ between 1994–1998 and 1999–2004 (HR 1.46, 95% CI 0.46–4.63), but showed continued declines in 2005–2010 (HR 0.13, 95% CI 0.04–0.41 vs 1999–2004; Supplementary Table 6, available from the authors on request).

In multivariable analysis, standard therapy was independently associated with lower risk of ESRD (adjusted HR 0.72, 95% CI 0.52–0.98, p = 0.04; Table 3). Variables of renal damage at biopsy (renal function, AI, and CI) and male sex were independently associated with higher risk of ESRD. After adjustment for patient demographic (age and sex), clinical characteristics (duration of LN, serum creatinine, and pathologic features), and treatment regimens used in the multivariable Cox regression, the more recent time period

Table 2. The treatment regimens for LN patients at different time periods.

Treatment Regimens	1994–1998, n = 179	1999–2004, n = 570	2005–2010, n = 1159	p
Immunosuppressive agents				
CYC	45 (25.1)	172 (30.2)	254 (21.9)	< 0.001
CNI	22 (12.3)	87 (15.3)	47 (4.1)	< 0.001
MMF	19 (10.6)	109 (19.1)	242 (20.9)	0.005
Combination therapy[a]	0 (0.0)	6 (1.1)	257 (22.2)	< 0.001
AZA	0 (0.0)	4 (0.7)	13 (1.1)	0.28
LEF	0 (0.0)	4 (0.7)	56 (4.8)	< 0.001
Corticosteroids only	11 (6.1)	24 (4.2)	44 (3.8)	0.34
TW + corticosteroids	80 (44.7)	164 (28.8)	244 (21.1)	< 0.001
Others[b]	2 (1.1)	0 (0.0)	2 (0.2)	0.06
ACEI/ARB	29 (16.2)	273 (47.9)	573 (49.4)	< 0.001

Values are n (%) unless otherwise specified. [a] Combined therapy consisted of corticosteroids, MMF, and tacrolimus. [b] Immunosuppressive agent was unknown or was not used. LN: lupus nephritis; CYC: cyclophosphamide; CNI: calcineurin inhibitors; MMF: mycophenolate mofetil; AZA: azathioprine; LEF: leflunomide; TW: *Tripterygium wilfordii*; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

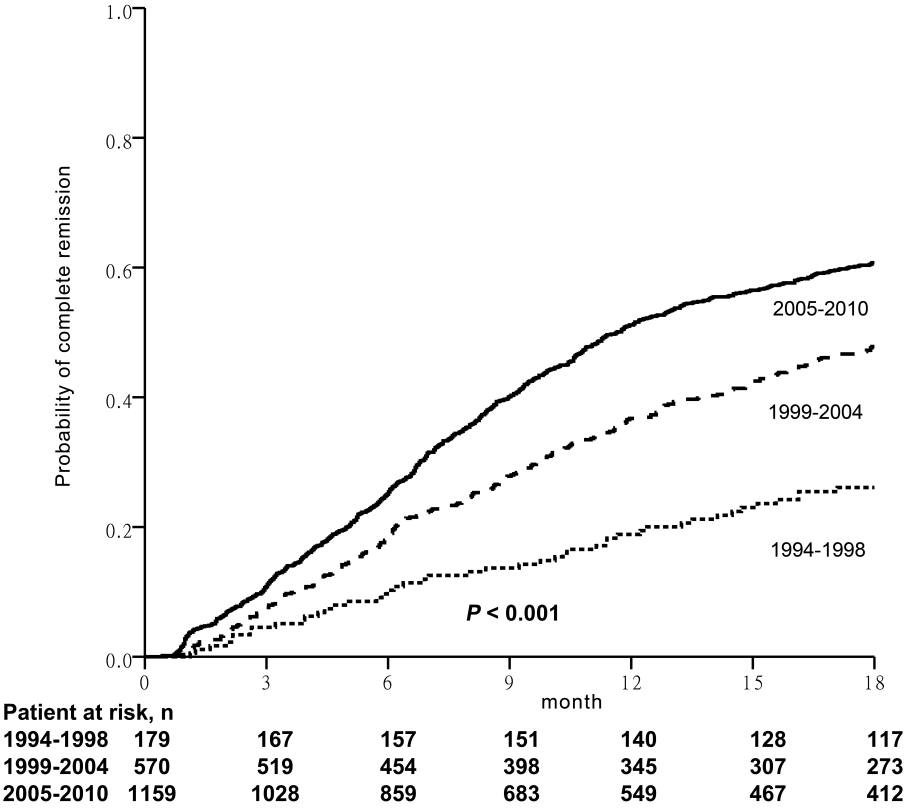

Figure 1. Kaplan-Meier curves of the probability of achieving complete lupus nephritis remission in the 3 time periods.

was not independently associated with a better prognosis (Table 3).

DISCUSSION

Our study showed the changes in patient characteristics, treatment, therapeutic effects, and outcomes of patients with LN from 1994 to 2010. We found that patients in the later time periods had shorter duration of disease, and presented with higher average GFR and lower chronicity at biopsy (more reversible disease). They also had more frequent followup and were more likely to receive standard-of-care therapies, which included CYC, MMF, or combination therapy. During these periods, response rates to induction therapies increased and renal relapse rates decreased. The longterm outcome trends were positive; the renal survival rates increased and the ESRD risk declined across the study periods, mainly in 2005–2010.

Several studies have evaluated the trends in outcomes of patients with LN, but whether the longterm outcome has improved over time is still a matter of debate[2,3,21,22,23,24,25]. One study evaluated trends in rates of ESRD from LN between 1995 and 2010 using the US Renal Data System. The authors found that the rate of endstage LN had stopped increasing and had declined from 1995 to 2010[26]. However, studies are unavailable for Chinese patients with LN. Racial and ethnic variations have been well described in the prevalence, presentation, and prognosis of patients with LN[27]. Asian patients seemed more likely to have renal involvement and to have a higher severity of disease compared with whites[28]. And clinical practice and outcomes of LN may vary among different racial backgrounds and geographical regions. Therefore, it is meaningful to evaluate the trends in treatment modalities and outcomes of Chinese patients with LN.

It is encouraging to observe the positive trends in outcomes during the 17-year period of our study. There were several factors that likely led to better outcomes in the later groups. One of the reasons is earlier treatment of LN in the later time periods. Delay in diagnosis and treatment are associated with poor prognosis in patients with LN[21]. Our study showed that the duration of LN before diagnosis was longer in the earlier groups, suggesting late detection and treatment of disease. The delay in diagnosis is also supported by the finding that patients in the earlier period had a higher level of serum creatinine and a higher CI at biopsy. Therefore, chronic disease and late conditions were more common in the earlier periods, while patients in the later periods presented with more reversible disease at biopsy. And the increased serum creatinine level and histological signs of chronicity at presentation are important factors associated with ESRD in LN[17].

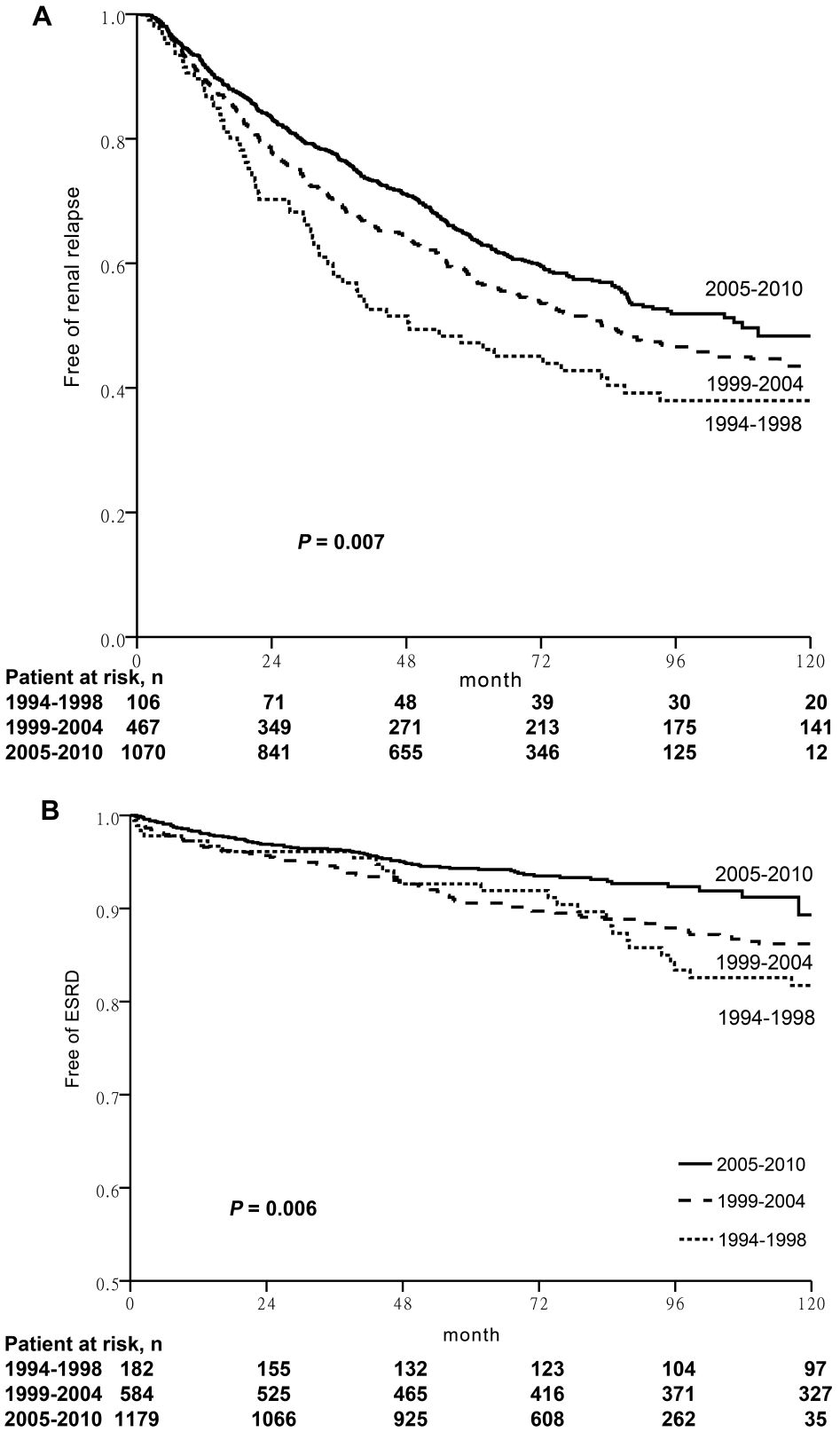

Figure 2. Kaplan-Meier estimates of (A) the probability of patients without renal flare, and (B) renal survival at different time periods (1994–1998, 1999–2004, and 2005–2010). ESRD: endstage renal disease.

Table 3. Multivariable Cox regression model for ESRD.

Covariates	Adjusted HR (95% CI)	p
Time period		0.14
2005–2010	1 (reference)	
1999–2004	1.35 (0.96–1.88)	
1994–1998	0.97 (0.61–1.52)	
Age	0.99 (0.98–1.00)	0.15
Female	0.66 (0.47–0.94)	0.02
Duration of LN	1.001 (0.997–1.005)	0.64
Serum creatinine	1.58 (1.47–1.70)	< 0.001
Activity index	1.05 (1.01–1.09)	0.007
Chronicity index	1.31 (1.23–1.39)	< 0.001
Standard therapy	0.72 (0.52–0.98)	0.04

ESRD: endstage renal disease; LN: lupus nephritis.

Another reason for the better prognosis in later time periods might be the socioeconomic factors. The relationship between socioeconomic status and SLE prognosis has been examined. One study showed that poverty was positively associated with SLE mortality and LN progression, independent of race or ethnicity[29,30]. Those who had private insurance and/or Medicare health coverage also had a less active SLE at diagnosis[31]. China has undergone a rapid economic and sociocultural change in recent years and has expanded its government insurance schemes. The basic medical insurance scheme, which covered urban workers, was established at the end of 1998 and the resources for rural healthcare increased greatly after 2003[32]. According to the National Health Services Survey, between 2003 and 2011 insurance coverage increased from 29.7% to 95.7%[33]. These advances in the Chinese healthcare system over recent years might have increased access to medical care and have improved LN outcomes.

Clinical trials of induction therapies for LN have also been carried out in China over the past decades[11,12,13,34,35]. In our study, we reviewed the various treatments over a 17-year period and observed great changes in treatment modalities. The majority of patients in the period of 1994 to 1998 did not receive the standard of care for LN (CYC) at the time. Patients in the later groups were more likely to receive standard-of-care therapies (including CYC, MMF, or combination therapy). In line with this trend, the remission rates significantly increased and the rates of renal flare decreased. Nonresponse to therapy and recurrence are associated with poor prognosis in LN[36,37]. More importantly, we observed an independent association between standard therapy and renal outcome. Therefore, the better management of LN can also be taken as one explanation for better outcome in the later periods. In addition to the increased use of induction therapies, it is also necessary to point out the significant increase in the use of ACEI/ARB and their possible influence on the outcome. ACEI/ARB are important adjunct treatments for LN, and have been shown to have antiproteinuric effects and to reduce progression of chronic kidney disease[38,39]. Although the use of these treatments has increased, there is still some room for improvement.

We also observed that the rates of renal relapse decreased and the median followup frequency increased from 1.6 (IQR 1.1–2.4) visits per year in 1994–1998, to 3.3 (IQR 2.5–4.4) visits per year in 2005–2010. These data suggest that patient compliance has improved. The increase in followup frequency might be attributed to recent improvement in patient management systems. Specialized outpatient departments were created for LN patients to improve patient healthcare services in 2003. In addition, patient profiles have become more detailed since the electronic medical system came into use in the early 2000s at the center. Patient management systems have become more standardized and specialized, and might be helpful for increasing adherence rates. Renal relapse is common in LN and associated with ESRD development[37], so early recognition and treatment of recurrence is crucial. Also, regular followup is a potent way to monitor the disease and determine adjustments to the therapy. Therefore, more frequent followup in the later groups might also contribute to the improvement of outcomes.

There are some limitations to our study. First, there was a lack of information on maintenance therapy, which is important to prevent renal relapse and to reduce the risk of chronic kidney disease development. However, it is difficult to collect and describe these kinds of data, because each patient may have changed regimens several times during the maintenance period. In addition, there was a lack of information on adverse events. Prior to 2003, the adverse events records were incomplete; therefore, any adverse events comparisons may lead to false conclusions. Also, the number of patients in the first study period was relatively small, which may lead to the possibility of bias. In addition, data from our study were acquired from a single center. Finally, the variables (such as medical insurance, household income, education) of socioeconomic status were unavailable for most of the patients. This center is the biggest national clinical center for kidney diseases in China. Although the cohort has a large sample size and the patients came from a variety of regions in China, the participants may not have been an adequate representation of the entire Chinese population.

Our study shows that the outcomes of Chinese patients with LN have improved from 1994 to 2010. During this period, the use of standard-of-care therapies has increased greatly. In line with this trend, remission rates have increased and renal relapse has decreased.

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