Improvement of outcomes in patients with lupus nephritis: management evolution in Chinese patients from 1994 to 2010

Si-Jia Shao*, Jin-Hua Hou*, Guo-Tong Xie, Wen Sun, Dan-Dan Liang, Cai-Hong Zeng, Hui-Xian Zhu, Zhi-Hong Liu

*Si-Jia Shao and Jin-Hua Hou contributed equally to this article as the co-first author.

ABSTRACT

Objective. To assess how the long-term outcomes has 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 LN patients (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 follow-up. They were more likely to receive standard of care therapies, which included cyclophosphamide, mycophenolate mofetil and combined 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 end-stage renal disease (ESRD) did not differ between 1994-1998 and 1999-2004, but was significantly lower in 2005-2010 (hazard ratio 0.40 [95% confidence interval, 0.19-0.85] versus 1999-2004). In multivariable COX analysis, standard therapy was independently associated with lower risk of ESRD (adjusted OR 0.70, 95% CI 0.51–0.97, P=0.034). Parameters of renal damage at biopsy (renal function, AI and CI) 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.

Key Indexing Terms: Lupus nephritis, remission, outcomes.

Author Affiliations: From the National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China; IBM Research-China, Beijing, China

Funding: This research was funded by the National Key Technology R&D Program (2015BAI12B05) and the National Key Research and Development Program (2016YFC0904100) by the Ministry of Science and Technology of the People's Republic of China.

Authors and Affiliations: S.J. Shao, MD; J.H. Hou, MD; D.D. Liang, MD; C.H. Zeng, MD; H.X. Zhu, MD; Z.H. Liu, MD, National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine. G.T. Xie, PhD; W. Sun, PhD, IBM Research-China.

Corresponding Author: Prof. Zhi-Hong Liu, National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, 305 East Zhongshan Road, Nanjing 210002, China. Phone: 86-25-84801992. E-mail: liuzhihong@nju.edu.cn.

Running title: Lupus nephritis in China

INTRODUCTION

Lupus nephritis (LN), which affects over half of systemic lupus erythematosus (SLE), has a negative impact on the disease[1]. Up to 25 percent of patients with LN will progress to end-stage renal disease (ESRD) within 10 years after their diagnosis[2-5]. 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 depends on the degree of response to treatment; thus, tremendous efforts have been made to develop effective treatment over the past decades[7]. A number of regimens have been assessed in clinical trials such as cyclophosphamide (CYC)[8], mycophenolate mofetil (MMF)[9], calcineurin inhibitors (CNIs)[10, 11], combined therapy (combining corticosteroids, MMF, and tacrolimus)[12, 13], and biologic agents[14, 15]. Besides 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, the healthcare policy and healthcare access play a substantial role in outcomes of LN[17]. It was reported that socioeconomic factors such as limited access to specialized health care and lack of health insurance, can also result in poor prognosis[18]. China has undergone a rapid economic and sociocultural change with improvements to health system during the past 20 years. Medical care and outcomes may have also changed a lot among patients with LN in China.

The main purpose of this study was to investigate how the long-term outcomes of LN have changed during the past two decades. Trends in patient manifestation and renal damage at diagnosis, treatment regimens, treatment response, relapse of disease and follow up frequency

were evaluated using the data from Nanjing Glomerulonephritis Registry from 1994 to 2010. We tried to quantify the impact of the change of the treatment modalities into clinical practice on outcome, and examined the independent association between standard therapies and renal outcome

MATERIALS AND METHODS

Study Population

This study evaluated LN patients in the Nanjing Glomerulonephritis Registry at the National Clinical Research Center of Kidney Diseases, Jinling Hospital from January 1994 to December 2010. All LN patients diagnosed through a renal biopsy at the center were included in the registry. Patients were included in this 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 who were 14 years or younger (173), who had incomplete inpatient and outpatient records (20), and who had a follow-up duration less than 12 months without ESRD (138) were excluded from this study, 1945 patients were included 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, including demographic characteristics (age, gender), medical history (duration of SLE and LN, prior treatment with immunosuppressive agents, prior dialysis, prior renal biopsy), clinical severity (hypertension, anemia, hypoalbuminemia, SLE Disease Activity Index [SLEDAI], urinary protein, urine sediment RBC count, serum creatinine,

estimated glomerular filtration rate [eGFR], uric acid, serum C3, serum C4, anti-double-stranded DNA [anti-ds DNA]), and pathological characteristics (pathologic classification, activity index [AI], chronicity index [CI]) were examined. 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-2000 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.

Follow-up information including clinical parameters and important lab tests were monitored and recorded at every visit. Data was collected by trained physicians accustomed with standardized case report forms.

Outcomes

This study focused on changes over time in medical practice, treatment response, renal relapse, and renal survival. Medical care practice included immunosuppressive agents (CYC, MMF, CNIs, combined therapy, azathioprine [AZA], leflunomide [LFM], *Tripterygium wilfordii* [TW]) and non-immunosuppressive therapies (angiotensin converting enzyme inhibitors/angiotensin receptor blockers [ACEI/ARB]). Details of the standard induction therapy protocol for LN in our center were available in Supplementary Appendix A. The primary end point of the study was ESRD, which was defined as eGFR of less than 15 mL/min/1.73 m^2 for at least three 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-hour urinary protein $\leq$ 0.4 g/d, the absence of active urine sediments, serum albumin $\geq$ 35 g/L, and normal serum creatinine levels. Partial remission was defined as a $\geq$ 50% reduction in proteinuria and urinary protein <3.5 g/d, serum albumin level $\geq$ 30g/L, and normal or $\leq$ 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 in this analysis[20].

Statistical Analysis

Patients were stratified into three 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 (IQRs). 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 by using Kaplan-Meier method and were compared by 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 were used to derive the hazard ratios (HRs) 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, gender) 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 multivariable COX model. All statistical tests were 2-tailed, and *P*-values were significant at 0.05 or less. 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 from 1994-1998, 584

from 1999-2004, 1179 from 2005-2010). The median follow-up duration was 81.7 months (IQR, 55.2-116.0).

Table 1 showed 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 former period were more likely to present with hypoalbuminemia and had higher serum creatinine concentration. Patients in later periods had higher levels of SLE-DAI 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 three 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-ds DNA. The gender, previous treatment with immunosuppressive agents, history of dialysis and anemia rate did not significantly change from 1994 to 2010. The median follow-up 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.

The trends in renal pathologic features of these patients were also showed 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 former period.

Treatment Regimens 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 combined therapy in 2005 (Supplementary Figure 1), 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 combined therapy increased from 0% to 22.2% (P < 0.001). Meanwhile, the use of CNIs decreased from 12.3% to 4.1% (P < 0.001). The rates of TW combined with corticosteroids decreased from 44.7% to 22.1% (P < 0.001). The number of patients who received AZA or LFM was small (17 patients received AZA and 60 received LFM). The use of ACEI/ARB also increased significantly across the study periods (P < 0.001) (Table 2). Patients with proliferative LN had similar trends in treatment modalities (Supplementary Table 1). In class II and class V LN, corticosteroids with TW were the most commonly used therapy (Supplementary Table 2 and 3).

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 patents 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, 2005-2010, respectively (P < 0.001). The cumulative probabilities of complete remission at 6 months for the three 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 HRs were 2.05 [95% CI, 1.57-2.67] and 2.92 [95% CI, 2.26-3.76]; Supplementary Table 4).

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 HRs 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).

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) of patients in 1999-2004, and 6.4% (76/1179) of patients in 2005-2010. The 5-year renal survival rates were 92.6% (CI, 87.4%-95.8%), 90.6% (CI, 87.8%-92.8%) and 94.3% (CI, 92.7%-95.5%) for the periods of 1994-1998, 1999-2004 and 2005-2010, respectively (1994-1998 versus 1999-2004, P = 0.52; 1994-1998 versus 2005-2010, P = 0.009; 1999-2004 versus 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 hazard ratio of ESRD in 2005-2010 appeared to be significantly lower than 1999-2004 After 5 years of follow-up, the adjusted HRs for ESRD was 0.76 (95% CI, 0.32-1.85) in 1994-1998 (versus 1999-2004) and 0.40 (95%CI, 0.19-0.85) in 2005-2010 (versus 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], versus 1999-2004) (Supplementary Table 6).

In multivariable analysis, standard therapy was independently associated with lower risk of ESRD (adjusted HR 0.72, 95% CI 0.0.52–0.98, P=0.04). Parameters of renal damage at biopsy (renal function, AI and CI) and male were independently associated with higher risk of ESRD. After adjustment for patient demographic (age and gender), clinical characteristics (duration of LN, serum creatinine and pathologic features) and treatment regimens used in the multivariable COX regression, the recent time period was not independently associated with a better prognosis (Table 3).

DISCUSSION

This study showed the changes in patient characteristics, treatment, therapeutic effects, and outcomes of patients with lupus nephritis 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 follow up and were more likely to receive standard of care therapies, which included CYC, MMF, or combined therapy. During this period, response rates to induction therapies have increased and renal relapse rates have decreased. The long-term outcome trends were positive as 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 long-term outcome has improved over time is still a matter of debate[2, 3, 21-25]. One study evaluated trends in rates of ESRD from LN between 1995 and 2010 with the U.S. Renal Data System. The authors found that the rate of end-stage LN had stopped increasing and had declined in the last decade[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 LN patients[27]. Asian patients seemed more likely to have renal involvement and have a higher severity of disease compared with Caucasians[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 LN patients.

It's encouraging to observe the positive trends in outcomes during this 17-year period. There were several factors that likely led to better outcomes in the later groups. One of the reasons is an earlier treatment of LN in the later time periods. Delay in diagnosis and treatment are associated with poor prognosis in patients with LN[21]. This study showed that

the duration of LN before diagnosis was longer in the earlier groups, suggesting a 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 chronicity index 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].

Another reason for the better prognosis in later time periods might be the socioeconomic factors. The relationship between socioeconomic status and lupus prognosis have 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 Chinese healthcare system over the past decades might have increased access to medical care and have positively influenced LN outcomes.

Clinical trials of induction therapies for LN have also been carried out in China over the past decades[11-13, 34, 35]. In this study, we reviewed the various treatments over this 17-year period and great changes of treatment modalities were observed. The majority of patients in the period of 1994-1998 did not receive the standard of care for LN (CYC) at the time. And patients in the later groups were more likely to receive standard of care therapies (which included CYC, MMF, or combined therapy). Current with this trend, the remission rates

significantly increased and the rates of renal flare decreased. Non-response 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. Besides the increased use of induction therapies, it is also necessary to point out the significant increase in the use of ACEI/ARBs and its possible influence on the outcome. ACEI/ARBs are important adjunct treatments for LN, which have been shown to have antiproteinuric effects and 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 follow-up 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 of follow-up frequency might be attributed to the improvement of patient management system in recent decades. Specialized outpatient departments were created for LN patients to improve patient health care services in 2003. In addition, patient profiles have become more detailed since electronic medical system came into use in the early 2000s at the center. Patient management system has become more standardized and specialized, which 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. And regular follow-up is a potent way to monitor the disease and adjust the therapy. Therefore, more frequent follow-up in the later groups might also contribute to the improvement of outcomes.

There are some limitations to this study. First, there was a lack of information on maintenance therapy, which is important to prevent renal relapse and to reduce the risk of CKD development. However, it is difficult to collect and describe this kind of data, because

each patient may have changed their 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 this study was acquired from a single center. Finally, the parameters (such as medical insurance, household income, education) of the socioeconomic status were unavailable for most of the patients. It is the biggest national clinical center of kidney diseases in China. Although the cohort has 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.

In conclusion, this 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. Current with this trend, the remission rates have increased and renal relapse have decreased.

ACKNOWLEDGMENTS

The authors thank Fei Gu (Medical Pfizer Investment Co. Ltd., Beijing, China) and Meizhen Xiang (Aiyidata Research, Beijing, China) for editorial assistance.

Disclosure statement: The authors have declared no conflicts of interest.

REFERENCES

1. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550-7.

2. Donadio JV, Hart GM, Bergstralh EJ, Holley KE. Prognostic determinants in lupus nephritis: a long-term clinicopathologic study. Lupus 1995;4:109-15.

3. Bono L, Cameron JS, Hicks JA. The very long-term prognosis and complications of lupus nephritis and its treatment. Q J Med 1999;92:211-8.

4. Kono M, Yasuda S, Kato M, Kanetsuka Y, Kurita T, Fujieda Y, et al. Long-term outcome in Japanese patients with lupus nephritis. Lupus 2014;23:1124-32.

5. Yang J, Liang D, Zhang H, Liu Z, Le W, Zhou M, et al. Long-term renal outcomes in a cohort of 1814 Chinese patients with biopsy-proven lupus nephritis. Lupus 2015;24:1468-78.

6. Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. Arthritis Rheum 2013;65:2154-60.

7. Chan TM. Treatment of severe lupus nephritis: the new horizon. Nat Rev Nephrol 2015;11:46-61.

8. Austin HA 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614-9.

9. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156-62.

10. Austin HA 3rd , Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol 2009;20:901-11.

11. Chen W, Tang X, Liu Q, Chen W, Fu P, Liu F, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial. Am J Kidney Dis 2011;57:235-44.

12. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. J Am Soc Nephrol 2008;19:2001-10.

13. Liu ZH, Zhang HT, Liu ZS, Xing CY, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med 2015;162:18-26.

14. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215-26.

15. ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. Arthritis Rheum 2014;66:3096-104.

16. Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Am J Kidney Dis 2000;35:904-14.

17. Davidson A. What is damaging the kidney in lupus nephritis? Nat Rev Rheumatol 2016;12:143-53.

18. Ward MM. Medical insurance, socioeconomic status, and age of onset of endstage renal disease in patients with lupus nephritis. J Rheumatol 2007;34:2024-7.

19. 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.

20. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guidelines for glomerulonephritis. Kidney Int Suppl 2012;2:139-274.

21. Fiehn C, Hajjar Y, Mueller K, Waldherr R, Ho AD, Andrassy K. Improved clinical

outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment. Ann Rheum Dis 2003;62:435-9.

22. Faurschou M, Dreyer L, Kamper AL, Starklint H, Jacobsen S. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. Arthritis Care Res (Hoboken) 2010;62:873-80.

23. Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. Rheumatology (Oxford) 2011;50:1424-30.

24. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant 2012;27:3248-54.

25. Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P, Ponticelli C. Progressive improvement of patient and renal survival and reduction of morbidity over time in patients with lupus nephritis (LN) followed for 20 years. Lupus 2013;22:810-8.

26. Sexton DJ, Reule S, Solid C, Chen SC, Collins AJ, Foley RN. ESRD from lupus nephritis in the United States, 1995-2010. Clin J Am Soc Nephrol 2015;10:251-9.

27. Korbet SM, Schwartz MM, Evans J, Lewis EJ, Collaborative Study G. Severe lupus nephritis: racial differences in presentation and outcome. J Am Soc Nephrol 2007;18:244-54.

28. Mok MY, Li WL. Do Asian patients have worse lupus? Lupus 2010;19:1384-90.

29. Walsh SJ, DeChello LM. Geographical variation in mortality from systemic lupus erythematosus in the United States. Lupus 2001;10:637-46.

30. Barr RG, Seliger S, Appel GB, Zuniga R, D'Agati V, Salmon J, et al. Prognosis in proliferative lupus nephritis: the role of socio-economic status and race/ethnicity. Nephrol Dial Transplant 2003;18:2039-46.

31. Karlson EW, Daltroy LH, Lew RA, Wright EA, Partridge AJ, Roberts WN, et al. The independence and stability of socioeconomic predictors of morbidity in systemic lupus erythematosus. Arthritis Rheum 1995;38:267-73.

32. Hu S, Tang S, Liu Y, Zhao Y, Escobar ML, de Ferranti D. Reform of how health care is paid for in China: challenges and opportunities. Lancet 2008;372:1437.

33. Meng Q, Xu L, Zhang Y, Qian J, Cai M, Xin Y, et al. Trends in access to health services and financial protection in China between 2003 and 2011: a cross-sectional study. Lancet 2012;379:805-14.

34. Hu WX, Liu ZH, Chen HP, Tang Z, Wang QW, Shen KQ, et al. Mycophenolate mofetil vs cyclophosphamide therapy for patients with diffuse proliferative lupus nephritis. Chin Med J (Engl) 2002;115:705-9.

35. F L, Y T, X P, L W, H W, Z S, et al. A prospective multicentre study of mycophenolate mofetil combined with prednisolone as induction therapy in 213 patients with active lupus nephritis. Lupus 2008;17:622-9.

36. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 2004;50:3934-40.

37. Parikh SV, Nagaraja HN, Hebert L, Rovin BH. Renal flare as a predictor of incident and progressive CKD in patients with lupus nephritis. Clin J Am Soc Nephrol 2014;9:279-84.

38. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. Ann Intern Med 1997;127:337-45.

39. Kanda H, Kubo K, Tateishi S, Sato K, Yonezumi A, Yamamoto K, et al. Antiproteinuric effect of ARB in lupus nephritis patients with persistent proteinuria despite immunosuppressive therapy. Lupus 2005;14:288-92.

FIGURE LEGENDS

Figure 1. Probability of achieving complete remission in LN patients at different time periods. Kaplan-Meier curves of achieving complete remission according to the three time periods.

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

Table 1. Manifestation of LN patients at the time of renal biopsy

Time period (number)	1994-1998 (n=182)	1999-2004 (n=584)	2005-2010 (n=1179)	*P* value
Demographics				
Age at biopsy, *y*	29.4 (24.8-34.7)	30.6 (24.4-36.6)	31.8 (23.5-39.5)	< 0.001
Women, *n (%)*	157 (86.3%)	514 (88.0%)	1018 (86.3%)	0.60
Medical history				
Duration of SLE, *mo*	26.1 (7.2-66.0)	19.3 (5.2-59.5)	20.1 (4.0-61.7)	0.03
Duration of LN, *mo*	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, *n (%)*	149 (81.9%)	447 (76.5%)	872 (74.0%)	0.08
Prior renal biopsy, *n (%)*	3 (1.6%)	34 (5.8%)	155 (13.1%)	< 0.001
Prior dialysis, *n (%)*	0 (0.0%)	6 (1.0%)	26 (2.2%)	0.06
Clinical severity				
SLE-DAI	10.0 (7.0-13.0)	12.0 (8.0-14.0)	12.0 (10.0-16.0)	< 0.001
Hypertension, *n (%)*[a]	83 (45.6%)	215 (36.8%)	426 (36.1%)	0.05
Anemia, *n (%)*[b]	152 (83.5%)	468 (80.1%)	921 (78.1%)	0.20
Hypoalbuminemia, *n (%)*[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, *n (%)*[d]				
≥90 mL/min/1.73 m^2	71 (39.0%)	301 (51.5%)	756 (64.1%)	< 0.001
60-89mL/min/1.73 m^2	54 (29.7%)	156 (26.7%)	201 (17.0%)	< 0.001
30-59mL/min/1.73 m^2	34 (18.7%)	78 (13.4%)	148 (12.6%)	0.08
<30 mL/min/1.73 m^2	23 (12.6%)	49 (8.4%)	74 (6.3%)	0.006
Urinary protein, *g/d*	1.94 (1.18-2.96)	2.58 (1.24-5.15)	2.39 (1.20-4.37)	< 0.001
Urinary protein, *n (%)*				
<0.4 g/d	6 (3.3%)	31 (5.3%)	58 (4.9%)	0.54
0.4-3.49 g/d	144 (79.1%)	326 (55.8%)	708 (60.1%)	< 0.001
≥3.5 g/d	32 (17.6%)	226 (38.7%)	413 (35.0%)	< 0.001
Urine RBC, $\times 10^4/ml$	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, *n (%)*	92(50.5%)	248(42.5%)	626(53.1%)	< 0.001
Pathologic features				
Pathologic classification, *n (%)*				
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 activity index	8.0 (3.0-11.0)	6.0 (2.0-10.0)	7.0 (2.0-11.0)	0.05
Pathologic chronicity index	2.0 (1.0-4.0)	2.0 (0.0-3.0)	2.0 (0.0-3.0)	0.05
High AI (AI ≥ 12)	38 (20.9%)	100 (17.1%)	233 (19.8%)	0.34
High CI (CI ≥ 4)	49 (26.9%)	108 (18.5%)	217 (18.4%)	0.02
Follow-up frequency, *visits/year*	1.6 (1.1-2.4)	2.4 (1.7-3.2)	3.3 (2.5-4.4)	< 0.001

Abbreviations: SLE, systemic lupus erythematosus; LN, lupus nephritis; SLE-DAI, Systemic Lupus Erythematosus Disease Activity Index; eGFR, estimated glomerular filtration rate; Anti-ds DNA, anti-double-stranded DNA; AI, activity index; CI, chronicity index

[a] Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

[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 estimated glomerular filtration rate was calculated by 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. SCr=serum creatinine. SI conversion factors: To convert serum creatinine to μmol/L, multiply values by 88.4

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

Time period (number)	1994-1998 (n=179)	1999-2004 (n=570)	2005-2010 (n=1159)	*P* value
Immunosuppressive agents, *n (%)*				
CYC	45 (25.1%)	172 (30.2%)	254 (21.9%)	< 0.001
CNIs	22 (12.3%)	87 (15.3%)	47 (4.1%)	< 0.001
MMF	19 (10.6%)	109 (19.1%)	242 (20.9%)	0.005
Combined 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
LFM	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, *n (%)*	29 (16.2%)	273 (47.9%)	573 (49.4%)	< 0.001

Abbreviations: CYC, cyclophosphamide; CNIs, calcineurin inhibitors; MMF, mycophenolate mofeti; AZA, azathioprine; LFM, leflunomide; TW, *Tripterygium wilfordii*; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

[a] Combined therapy consisted of corticosteroids, MMF and tacrolimus.

[b] Immunosuppressive agent was unknown or was not used.

Table 3. Multivariable COX regression model for ESRD

Covariates	Adjusted hazard ratio (95% CI)	P-value
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
AI	1.05 (1.01-1.09)	0.007
CI	1.31 (1.23-1.39)	<0.001
Standard therapy	0.72 (0.52-0.98)	0.04

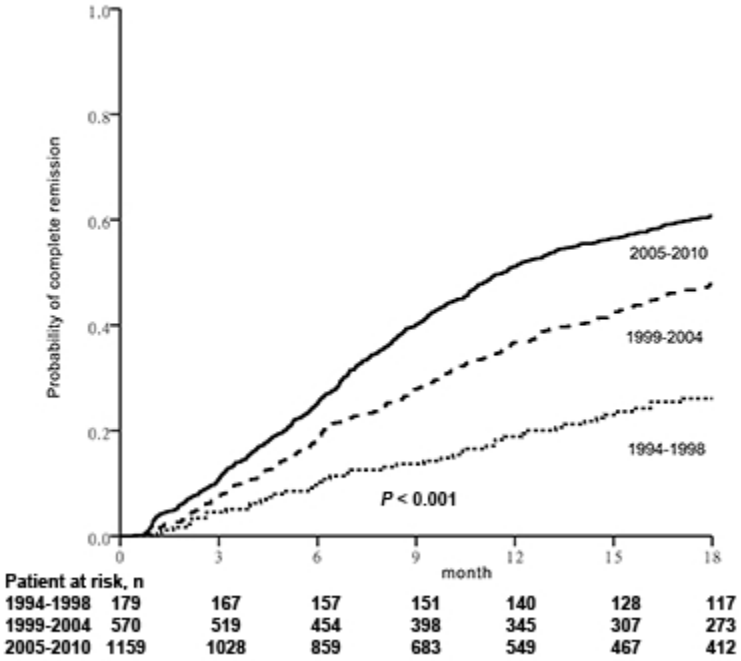

Figure 1. Probability of achieving complete remission in LN patients at different time periods. Kaplan-Meier curves of achieving complete remission according to the three time periods.

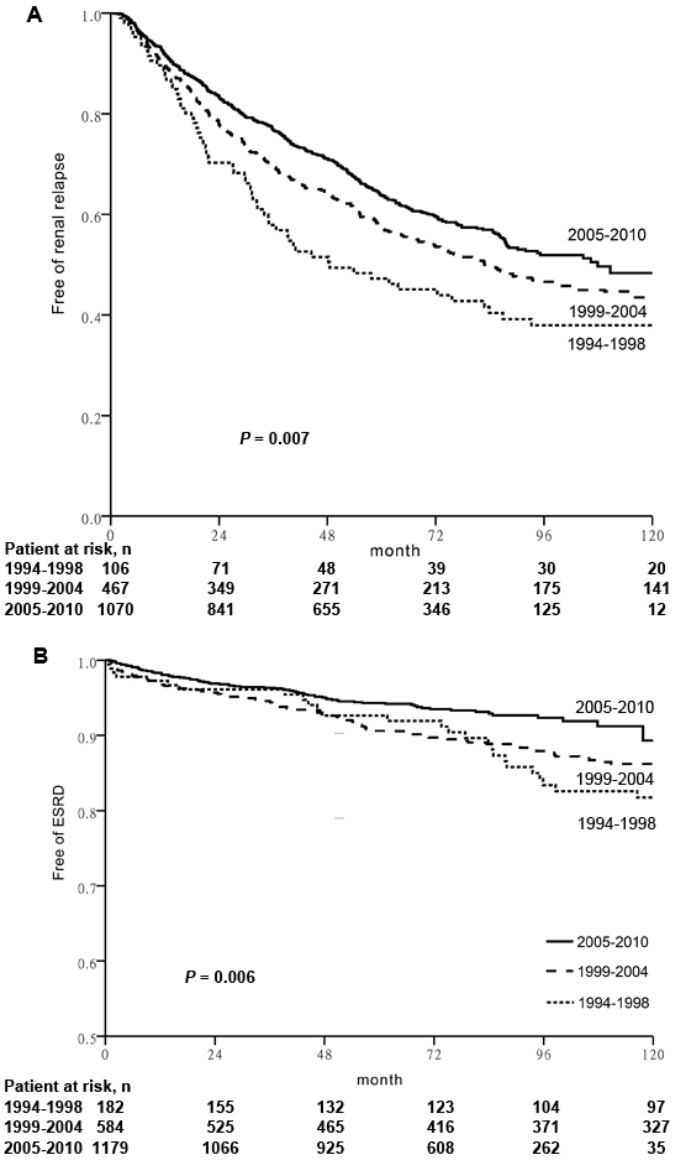

Figure 2. Kaplan-Meier estimates of (A) probability of patients without renal flare and (B) renal survival at different time periods (1994-1998, 1999-2004 and 2005-2010).