

Predictors of Longterm Mortality in Patients with and without Systemic Lupus Erythematosus on Maintenance Dialysis: A Comparative Study

HUNG-AN CHEN, JHI-JOUNG WANG, CHUNG-TEI CHOU, CHIH-CHIANG CHIEN, CHIN-CHEN CHU, MING-JEN SHEU, YEONG-JANG LIN, PEI-CHIH CHEN, and CHUN-HSIUNG CHEN

ABSTRACT. Objective. To compare the prognosis of patients with and without systemic lupus erythematosus (SLE) on dialysis and to determine the factors that affect survival after dialysis.

Methods. We used the Taiwan National Health Insurance Research Database (NHRI-NHIRD-99182) and collected data on patients who started maintenance dialysis between 2001 and 2003. Patients were followed from the initiation of dialysis until death, discontinuation of dialysis, or the end of 2008. We did a Kaplan-Meier analysis of the cohort and used multivariate Cox regression analysis to identify significant predictors of survival.

Results. Of the 22,394 dialysis patients studied, 303 (1.35%) had SLE. Hypertension and diabetes were the 2 most common comorbidities associated with dialysis for patients with and without SLE. After adjusting for age, sex, dialysis modality, and comorbidities, we found no significant survival difference between the 2 patient groups after 8 years of followup. Multivariate analysis showed that increased mortality in the patient group without SLE ($p < 0.05$) was associated with older age (≥ 45 years), male sex, initial choice of hemodialysis, diabetes mellitus, heart failure, coronary artery disease, cerebrovascular disease, and malignancy. In the patient group with SLE, independent predictors of mortality ($p < 0.05$) were older age (≥ 65 years), male sex, and diabetes mellitus.

Conclusion. The longterm survival outcome was similar between patients with and without SLE who were on dialysis. The factors affecting patient mortality were not identical in these 2 groups. (First Release Aug 15 2011; J Rheumatol 2011;38:2390-4; doi:10.3899/jrheum.110311)

Key Indexing Terms:

DIALYSIS MORTALITY OUTCOMES SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a broad range of clinical manifestations. The disease occurs predominantly in young women, with a peak age of onset between the late teens and early 40s, and a women-to-men ratio of 9:1¹. SLE is associated with a wide range of comorbidities caused by the disease, its treatment, or both. Renal involvement is common in SLE and nephropathy is a major cause of morbidity and mortality in patients with SLE². Despite recent advances in the

treatment of lupus nephritis, a significant number of patients will progress to endstage renal disease (ESRD) within 10 years³. Lupus nephritis is an important cause of ESRD. Clinical and serological disease activity has been reported to decrease in patients with SLE who have developed ESRD^{4,5}. However, ESRD is a costly and disabling condition with a high mortality rate^{6,7}.

Dialysis is the most common therapeutic modality for ESRD. Patients with SLE on dialysis are often young and female, factors that can influence survival⁵. There are conflicting data regarding the survival of patients with SLE during chronic dialysis therapy; their longterm survival on dialysis can be no different from that of patients on dialysis who do not have SLE^{4,8,9}. However, a recent study using a large national database showed that patients with ESRD secondary to SLE are at an increased risk of death compared with other patients with ESRD¹⁰.

It has been demonstrated that SLE is more common among Chinese than Whites^{11,12}. The incidence and prevalence rates of ESRD are also high in Taiwan⁷. However, little is known about the prognostic factors that affect survival after dialysis in Taiwanese patients with SLE. There are also few nationwide studies that analyze the survival of patients

From Chi-Mei Medical Center, Tainan; Buddhist Tzu Chi General Hospital, Taipei Branch; and Taipei Veterans General Hospital, Taipei, Taiwan.

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H-A. Chen, MD; J-J. Wang, MD, PhD, Chi-Mei Medical Center; C-T. Chou, MD, Professor of Rheumatology, Taipei Veterans General Hospital; C-C. Chien, MD; C-C. Chu, MD, PhD; M-J. Sheu, MD; Y-J. Lin, MD; P-C. Chen, MD, Chi-Mei Medical Center; C-H. Chen, Buddhist Tzu Chi General Hospital, Taipei Branch.

Address correspondence to Dr. C-C. Chien, Department of Nephrology, Chi-Mei Medical Center, 901 Jung-Hua Road, Yung Kang District, Tainan 710, Taiwan. E-mail: ccchien58@yahoo.com.tw

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with SLE on dialysis in Asia. To evaluate the outcomes of these patients, we used a large dataset from the Taiwan National Health Insurance Research Database (NHIRD) to compare the difference in mortality between patients with or without SLE on dialysis. Age and comorbidities presented at the onset of ESRD were analyzed to aid in the prediction of longterm mortality in patients on dialysis. Our specific goals were to identify risk factors for mortality and to compare the differences in these factors for patients with and without SLE who are on dialysis.

MATERIALS AND METHODS

Database. The Taiwan National Health Insurance (NHI) program, which provides compulsory universal health insurance, has been in place since 1995. With the exception of prison inmates, all citizens are enrolled in the program. All contracted medical institutions must submit standard claim documents for medical expenses on a computerized form. Patients with ESRD are eligible for any type of renal replacement therapy free of charge and without copayments; all patients on chronic dialysis are covered by the NHI program.

Data for our cohort study were obtained from the NHIRD (www.doh.gov.tw/statistic/index.htm [in Chinese]; http://www.doh.gov.tw/EN2006/index_EN.aspx [in English]). The data were released for research purposes by the Taiwan National Health Research Institute. The NHIRD, which includes nearly all (99%) inpatient and outpatient medical benefit claims for the Taiwanese population of 23 million, is one of the largest and most comprehensive databases in the world and has been used extensively in various studies. The NHIRD provides encrypted patient identification numbers, sex, date of birth, dates of admission and discharge, medical institutions providing the services, the ICD-9-CM (International Classification of Diseases-9-Clinical Modification) diagnostic (up to 5) and procedure codes (up to 5), and outcome. After obtaining ethics committee approval (NHRI-NHIRD-99182), we used the NHIRD for ambulatory care claims and all inpatient claims, and the updated registry for beneficiaries from 2001 to 2008. All datasets can be interlinked through each individual's unique personal identification number.

Patient selection and definition. We enrolled patients with ESRD, including patients under 18 years old, who initiated maintenance dialysis between January 1, 2001, and December 31, 2003. Patients on maintenance dialysis were defined as having undergone dialysis > 90 days. Patients who had undergone renal transplantation before the initiation of dialysis were excluded. The patients were followed from the day of their first dialysis treatment until death, end of dialysis, or the end of the followup period on December 31, 2008. A total of 22,394 incident dialysis patients were analyzed.

Demographic and comorbid variables. Patients with ESRD were stratified according to the presence or absence of SLE when they started dialysis treatment. The research focused not only on survival status, but also on date of death and demographic and comorbidity variables. The demographic variables such as age and sex and the initial dialysis modality were recorded. At baseline, major comorbidities affecting mortality, such as diabetes mellitus, hypertension, heart failure, coronary artery disease, cerebrovascular disease, peripheral artery disease, and malignancy, were recorded. Selected comorbidities were determined based on diagnostic codes in ambulatory visit or hospitalization databases at the start of dialysis. ICD-9-CM codes used to define clinical conditions are shown in Table 1.

Statistical analyses. All values are expressed as incidences (%). Comparisons of the groups with or without SLE were done using an independent t test for continuous variables, and chi-squared tests for categorical variables. Event-free survival was calculated using the Kaplan-Meier method, and differences were assessed using the log-rank test. Hazard ratios (HR) and 95% CI were calculated for each factor using Cox univari-

Table 1. ICD-9-CM codes used to identify clinical conditions.

Diabetes mellitus	250.*; 357.2; 362.0*; 366.41
Hypertension	362.11; 401.*-405.*; 437.2
Heart failure	428.0-428.43; 428.9; 398.91
Coronary artery disease	410.*-414.*
Cerebrovascular disease	430-438.*
Peripheral arterial disease	440.0-440.9; 38.13-38.18; 39.22-39.26; 39.28
Malignancy	140.*-208.*
Systemic lupus erythematosus	710

* Can be any number, or missing. ICD-9-CM: International Classification of Diseases-9-Clinical Modification.

ate analysis. Covariables for established risk factors were further assessed by Cox multivariate regression analysis to determine significant predictors for mortality. If not addressed, p values < 0.05 were considered significant. SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all data analyses.

RESULTS

Baseline demographic and clinical data. Table 2 lists the characteristics of the patients with ESRD at the start of dialysis in this cohort. Of 22,394 patients undergoing dialysis, 303 (1.35%) had SLE. Patients with SLE were predominantly women and younger than the other patients (39.4 ± 15.3 yrs vs 59.4 ± 14.2 yrs, respectively; $p < 0.001$). There were 14 (4.62%) and 94 (0.43%) patients < 18 years old in the SLE and non-SLE patient groups, respectively. More patients with SLE received peritoneal dialysis (PD) as the first treatment for ESRD. Of the patients with SLE, 7 (2.31%) on hemodialysis (HD) were switching to PD; and 29 (9.57%) on PD were switching to HD during the followup period. Of the non-SLE patient group, 126 (0.57%) patients on HD were switching to PD and 525 (2.38%) on

Table 2. Comparison of baseline demographic and clinical characteristics between dialysis patients with systemic lupus erythematosus (SLE) and without SLE. All data are percentages.

Characteristic	Dialysis with SLE, n = 303	Dialysis without SLE, n = 22091	p*
Age at dialysis, yrs			< 0.001
< 45	67.3	15.3	
45-64	23.8	44.4	
≥ 65	8.9	40.4	
Men	18.8	48.1	< 0.001
First modality of dialysis			< 0.001
Hemodialysis	77.6	93.1	
Peritoneal dialysis	22.4	6.9	
Diabetes mellitus	10.6	46.9	< 0.001
Hypertension	68.6	77.6	< 0.001
Heart failure	9.9	19.3	< 0.001
Coronary artery disease	5.6	22.1	< 0.001
Cerebrovascular disease	2.6	11.9	< 0.001
Peripheral arterial disease	4.6	2.7	0.05
Malignancy	2.6	5.5	0.029

* All p values statistically significant ($p < 0.05$).

PD were switching to HD during the followup period. Of the patients with SLE, 28 (9.24%) were shifting from HD to renal transplantation and 15 (4.95%) were shifting from PD to renal transplantation. Of the non-SLE patient groups, 859 (3.89%) were shifting from HD to renal transplantation, and 222 (1%) were shifting from PD to renal transplantation. Patients with SLE were more likely than those without to have renal transplantation. Hypertension was the most common comorbidity associated with dialysis for patients with SLE, followed by diabetes mellitus, heart failure, coronary artery disease, peripheral arterial disease, cerebrovascular disease, and malignancy. Hypertension and diabetes were the 2 most frequent comorbidities for patients starting dialysis who did not have SLE. Patients with SLE had fewer baseline comorbidities than patients without SLE, except for peripheral arterial disease.

Survival analysis. The Kaplan-Meier survival curves for dialysis patients with and without SLE are illustrated in Figure 1. The 1-year cumulative survival rate was 97.6% and the 5-year rate was 84.0% in patients with SLE. The 1-year rate was 92.7% and the 5-year rate 62.2% in patients without SLE. The log-rank test showed the difference in survival rates between the 2 groups. Although the crude survival was better in patients with SLE, there was no significant difference in longterm mortality between the 2 groups after adjustment for age, sex, dialysis modality, and comorbidities (Table 3).

Table 3. Cox regression estimates adjusted for age, sex, dialysis modality, and comorbidities of the association between SLE and all-cause mortality for all patients.

Group	Univariate Analysis HR (95% CI)	Multivariate Analysis HR (95% CI)
Without SLE (reference)	1	1
SLE	0.424 (0.331–0.544)*	1.015 (0.790–1.304)

* Statistical significance ($p < 0.05$). HR: hazard ratio; SLE: systemic lupus erythematosus.

Risk factors for mortality in dialysis patients with and without SLE. The risk factors for all-cause mortality in dialysis patients are presented in Tables 4 and 5. The multivariate Cox proportional hazards analysis of baseline data showed that the independent predictors of longterm mortality among patients without SLE were age ≥ 45 years, male sex, initial choice of HD, diabetes mellitus, heart failure, coronary artery disease, cerebrovascular disease, and malignancy. Hypertension was associated with decreased mortality in the non-SLE group. Age ≥ 65 years, male sex, and diabetes at baseline were risk factors for mortality in patients with SLE.

DISCUSSION

We found that the adjusted survival rate of patients with

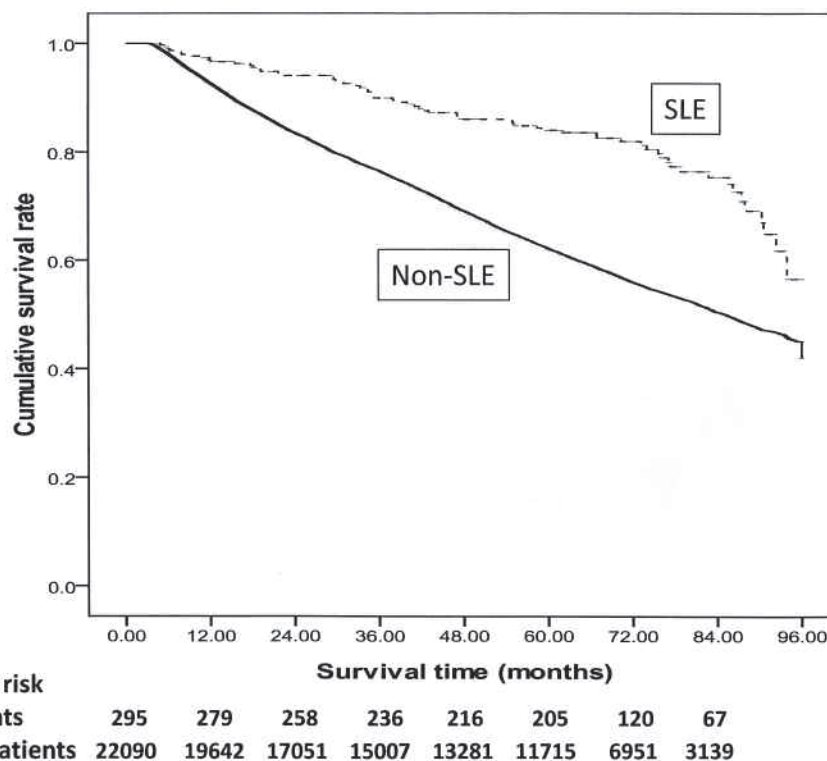


Figure 1. Kaplan-Meier survival curve of dialysis patients with and without SLE. The log-rank test showed a significant difference between the patient groups ($p < 0.001$).

Table 4. Univariate and multivariate Cox regression analyses of the predictors for all-cause mortality among dialysis patients with SLE. All p values are statistically significant ($p < 0.05$) except multivariate analysis of peripheral arterial disease.

Variable	Univariate Analysis HR (95% CI)	Multivariate Analysis HR (95% CI)
Age at dialysis, yrs		
< 45 (reference)	1	1
45–64	2.581 (2.354–2.829)	1.991 (1.813–2.185)
≥ 65	5.749 (5.254–6.291)	4.344 (3.960–4.765)
Sex, male vs female	1.141 (1.102–1.195)	1.228 (1.179–1.279)
First modality of dialysis,		
HD vs PD	0.699 (0.637–0.767)	1.142 (1.039–1.254)
Diabetes mellitus	2.243 (2.151–2.339)	1.881 (1.799–1.968)
Hypertension	1.394 (1.322–1.469)	0.937 (0.886–0.990)
Heart failure	1.910 (1.824–2.000)	1.390 (1.323–1.460)
Coronary artery disease	1.889 (1.807–1.974)	1.200 (1.144–1.258)
Cerebrovascular disease	1.901 (1.800–2.007)	1.377 (1.302–1.456)
Peripheral arterial disease	1.458 (1.305–1.628)	1.056 (0.945–1.181)
Malignancy	1.730 (1.600–1.871)	1.667 (1.540–1.804)

HR: hazard ratio; SLE: systemic lupus erythematosus; HD: hemodialysis; PD: peritoneal dialysis.

Table 5. Univariate and multivariate Cox regression analyses of the predictors for all-cause mortality among dialysis patients with SLE.

Variable	Univariate Analysis HR (95% CI)	Multivariate Analysis HR (95% CI)
Age at dialysis, yrs		
< 45 (reference)	1	1
45–64	1.551 (0.870–2.766)	1.176 (0.633–2.183)
≥ 65	3.741 (1.961–7.136)*	2.864 (1.348–6.085)*
Sex, male vs female	1.746 (1.000–3.050)*	1.795 (1.024–3.146)*
First modality of dialysis,		
HD vs PD	0.847 (0.452–1.590)	1.095 (0.567–2.115)
Diabetes mellitus	3.981 (2.298–6.897)*	2.979 (1.502–5.907)*
Hypertension	1.600 (0.883–2.899)	1.227 (0.659–2.282)
Heart failure	2.706 (1.440–5.087)*	1.407 (0.650–3.050)
Coronary artery disease	2.326 (1.056–5.125)*	0.866 (0.346–2.170)
Cerebrovascular disease	2.232 (0.698–7.137)	—
Peripheral arterial disease	0.321 (0.044–2.314)	—
Malignancy	1.773 (0.548–5.740)	—

* Statistical significance ($p < 0.05$). HR: hazard ratio; SLE: systemic lupus erythematosus; HD: hemodialysis; PD: peritoneal dialysis.

SLE on chronic dialysis was not different from that of patients without SLE who were on chronic dialysis during an 8-year followup period. It has been reported⁸ that the longterm clinical course of patients with SLE who have ESRD is similar to that of patients with ESRD associated with disorders other than SLE. A review article⁴ reported that the survival of patients with SLE who were on dialysis was comparable to that of patients without SLE who were on dialysis, and was perhaps better than that of patients with other autoimmune diseases. However, a small cohort

study¹³ found that patients with SLE on chronic dialysis had a lower survival rate than other patients with nondiabetic uremia in Taiwan. Another study¹⁴ also reported a higher mortality rate in patients with SLE on chronic PD compared with nondiabetic patients on chronic PD in Hong Kong. A recent analysis¹⁰ of data from the US Renal Data Systems found an increased risk of death in pediatric and adult patients with SLE on chronic HD compared with other patients on chronic HD. More studies are required to determine whether the presence of SLE is associated with excessive mortality in patients undergoing dialysis.

We have identified a number of baseline comorbidities that were significantly associated with longterm mortality in patients on dialysis who do not have SLE. Patient survival on dialysis has been associated with comorbid conditions when starting dialysis¹⁵. Older age and diabetes mellitus are well-known risk factors for mortality in patients with ESRD on dialysis^{6,16,17}. Other reported predictors of mortality in patients with ESRD are heart failure, coronary artery disease, cerebrovascular disease, and malignancy^{16,17}. The influence of blood pressure on the prognosis of patients on HD is controversial¹⁸. A “reversed J-shaped” relationship between blood pressure and mortality has been reported for patients on HD¹⁹. Our multivariate analysis showed that hypertension was not a mortality risk factor in patients with SLE on maintenance dialysis and that there was no significant interaction between hypertension and dialysis modality ($p = 0.140$). The description was the same for patients with SLE on either PD or HD treatment. Because there is little information about the influence of hypertension on the mortality of patients with SLE on dialysis, more studies are needed to confirm our finding. One study²⁰ reported a survival advantage for patients on PD during the first 2 years of dialysis treatment. We also found a survival advantage for PD as the first modality of dialysis in patients without SLE. Although gender is usually not considered a risk factor for mortality in patients on dialysis⁶, in our study the survival rate among men was worse than the rate among women, a result similar to a previous report²¹.

Patients with SLE have higher mortality rates than the general population. Nephritis and reduced creatine clearance at disease onset were found to be risk factors for longterm mortality in patients with SLE²². Renal damage seems to be the most important predictor of mortality in patients with SLE²³. Our multivariate Cox regression analysis revealed that male sex, older age, and the presence of diabetes mellitus when starting dialysis were predictive factors affecting the survival of patients with SLE on chronic dialysis. These factors were also the predictors of longterm mortality in patients without SLE on dialysis in our study. In contrast to one report²⁴, we did not find a poorer outcome in patients with SLE undergoing HD than in those undergoing PD.

It has been reported²² that male sex and older age at onset of SLE were associated with increased mortality in patients

with SLE and that the age when starting dialysis and transplantation significantly affected the survival of patients with ESRD due to SLE⁹. Comorbid diabetes when starting dialysis could affect the longterm survival of patients with SLE who have ESRD. A similar finding has been reported²⁵ in patients with SLE who are on longterm PD therapy: the prognosis depends on the severity of predialysis comorbidity, not SLE disease activity.

The strength of our study lies in its long followup interval, large population size, and high probability that nearly all relevant patients were collected from the database. However, our study is limited by its retrospective design, a lack of laboratory data, and a lack of information about the causes of death because they are not included in the Taiwan Bureau of National Health Insurance database. Detailed information specific to SLE and ESRD was also lacking. Further large prospective studies with detailed evaluations are needed to confirm our findings.

In our nationwide study, patients on dialysis who have SLE constituted a small fraction of the total population of patients on dialysis. After adjustment, there was no significant difference in longterm survival between the patients with SLE and the patients without SLE who were undergoing dialysis. The risk factors for longterm mortality were not identical in these 2 populations. Identifying patients at risk at the start of dialysis will enable treatment to be intensified, thus leading to better outcomes.

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