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Original Article

Long-term outcomes in lupus patients receiving different renal replacement therapy

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Abstract *Background/purpose:* To compare the long-term outcomes and survival rates of patients with end stage renal disease (ESRD) caused by lupus nephritis who received three different modalities of renal replacement therapy, including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT).

Methods: We retrospectively analyzed 94 patients with ESRD caused by lupus nephritis. Among these, 42 received HD, 12 received PD, and 40 underwent KT. The adverse events, survival data and cause of mortality were recorded.

Results: The mean age at onset of ESRD was younger in the KT group than in the HD group. Arteriovenous fistula (AVF) infection, sepsis, and AVF dysfunction were more common in the HD group than in the KT group. Peritonitis was more common in the PD group than in the HD group and KT group. Urinary tract infection was more common in the KT group than in the HD group. Cumulative survival rates were better in the KT group than in the HD or PD group.

Conclusion: The patients with ESRD caused by lupus nephritis who underwent KT had better long-term outcomes and survival rates than those who received HD or PD. This implies that KT is the better choice of renal replacement therapy in the patients with ESRD caused by lupus nephritis.

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Introduction

Lupus nephritis develops in 60% of patients with systemic lupus erythematosus (SLE).^{1–3} Despite advancements in its treatment, such as mycophenolate mofetil, lupus nephritis still progresses to end stage renal disease (ESRD) in approximately 20% of these patients and as a result, requires long-term renal replacement therapy.^{4,5} Over the past 35 years, kidney transplantation has become an established long-term therapy for patients with ESRD caused by lupus nephritis.⁶ Since these patients are younger than those with renal failure caused by other diseases, choosing the appropriate renal replacement therapy to achieve maximal survival and the best quality of life is very important.

Previous studies have shown that the results of kidney transplantation were similar in lupus patients and non-lupus patients.^{7–10} However, only a limited number of studies have compared the long-term outcomes in lupus patients receiving different modalities of renal replacement therapy, including kidney transplantation.¹¹ The aim of this retrospective study was to compare the long-term outcomes and survival rates of SLE patients with ESRD caused by lupus nephritis who received three different modalities of renal replacement therapy, including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT).

Methods

Patients

We analyzed 94 patients who received renal replacement therapy due to ESRD caused by lupus nephritis at National Taiwan University Hospital. All patients fulfilled at least four of the American College of Rheumatology criteria for the diagnosis of SLE. We collected data on gender, ages at onset of SLE and ESRD, age at the beginning of renal replacement therapy, interval from onset of SLE to ESRD, duration of renal replacement therapy, sources of kidney donation (living or cadaveric). The onset of ESRD was defined as the beginning of long-term dialysis. If the patient received both hemodialysis and peritoneal dialysis, they were assigned to the predominant treatment group (i.e., the one used longer during the follow-up period). We followed up the patients since the diagnosis of ESRD in the HD and PD groups and since kidney transplantation in the KT group.

Outcome measures

We recorded the adverse events during renal replacement therapy such as SLE flare-up, infection, cardiovascular

disease, malignancy, dysfunction of arteriovenous fistula (AVF) or peritoneal tube, and loss of grafted kidney. The survival data and cause of mortality were also analyzed.

Statistical analysis

Data was presented as means \pm standard deviation (SD). Kruskal Wallis test with post-hoc comparison, Pearson Chi-square, and Fisher's exact test were used to compare variables between different groups of patients. Kaplan-Meier analysis estimated survival functions since the beginning of renal replacement therapy. The log-rank test was applied to compare survival curves between different groups of patients. Multiple Cox regression analysis was used to estimate mortality hazard ratios after adjustment for potential confounders including age and sex. SPSS 21 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Graphpad Prism 5.04 statistical software (Graphpad Software Inc., San Diego, CA, USA) was used for survival analysis. A *p* value of <0.05 was considered statistically significant.

Results

Demographic characteristics

Among these patients, 42 received hemodialysis (HD), 12 received peritoneal dialysis (PD), and 40 underwent kidney transplantation (KT). The demographic data of these patients are shown in [Table 1](#). All three groups were predominantly female and had similar mean age at onset of SLE and age at the beginning of renal replacement therapy. The mean age at onset of ESRD was younger in the KT group than in the HD group ($p = 0.037$). There was no significant difference in the intervals from onset of SLE to ESRD and the duration of renal replacement therapy among the three groups.

Adverse events

SLE flare-up occurred in 9 patients (21%) of the HD group and in 3 patients (8%) of the KT group but not in the PD group ([Table 2](#)). There was no significant difference in the rate of SLE flare-up among the three groups. The manifestations of SLE flare-up included fever, central nervous system (CNS) lupus, thrombocytopenia, lupus nephritis, arthralgia, and serositis. One patient in the HD group had two flare-up episodes of fever and thrombocytopenia. One patient in the KT group had one episode of neuropsychiatric lupus and one of thrombocytopenia.

Sixteen patients (38%) of the HD group, 5 patients (42%) of the PD group, and 16 patients (40%) of the KT group experienced at least one episode of infection. The most

Table 1 Demographic characteristics of the patients.

	HD (n = 42)	PD (n = 12)	KT (n = 40)	p Value
Gender (male:female)	7:35	1:11	7:33	0.738
Age at onset of SLE (years)	27.9 ± 13.4	22.4 ± 9.2	22.1 ± 8.4	0.139
Age at onset of ESRD (years)	36.4 ± 14.1	33.2 ± 11.5	28.6 ± 9.7	0.037
Age at the beginning of RRT (years)	36.4 ± 14.1	33.2 ± 11.5	32.9 ± 10.1	0.637
Interval from SLE to ESRD (years)	8.5 ± 6.4	10.9 ± 6.8	6.4 ± 6.2	0.061
Duration of RRT (years)	6.3 ± 5.1	6.0 ± 5.2	7.1 ± 4.2	0.429

Data are presented as means ± SD.

ESRD = end stage renal disease; HD = hemodialysis; KT = kidney transplantation; PD = peritoneal dialysis; RRT = renal replacement therapy; SLE = systemic lupus erythematosus.

common infection was AVF infection in the HD group ($n = 7$; 17%), peritonitis in the PD group ($n = 4$; 33%), and urinary tract infection (UTI) in the KT group ($n = 8$; 20%). UTI was more common in the KT group than in the HD group ($p = 0.002$). AVF infection and sepsis were more common in the HD group than in the KT group ($p = 0.012$ and $p = 0.024$, respectively). Peritonitis was more common in

the PD group than in the HD group ($p = 0.018$) and KT group ($p = 0.008$).

Cardiovascular morbidity was more common in the HD group than in the KT group ($p = 0.001$). Cardiovascular morbidity included AVF dysfunction, aneurysm, thrombosis, arrhythmia, and hypertension crisis. Nineteen patients (45%) in the HD group had at least one episode of cardiovascular problems, most commonly AVF dysfunction. AVF dysfunction was more common in the HD group than in the KT group ($p < 0.001$). One patient in the KT group had one episode of AVF dysfunction during hemodialysis after the allograft was rejected. One patient in the HD group had coronary artery disease and dissecting aortic aneurysm, one patient in the HD group and one patient in the KT group had aortic aneurysm, and one patient in the KT group had left radial artery aneurysm. Two patients in the HD group and one patient in the KT group had thrombosis of superior vena cava, subclavian vein, and left innominate vein, respectively. One patient in the HD group developed atrial fibrillation, and one patient in the PD group had ventricular tachycardia and ventricular fibrillation ending in death.

Malignancy was noted in three patients receiving HD (renal cell carcinoma, large-B-cell lymphoma, and colon cancer, respectively), one patient in the PD group (breast cancer), and two patients in the KT group (cervical cancer in one and thyroid carcinoma and gastric cancer in the other).

Survival analysis

The cumulative survival rate in the patients receiving HD or PD was 92.4%, 90.4%, and 75.1% at 1, 5, and 10 years, respectively (Fig. 1). In comparison, the patients who underwent KT had better survival rates (100%, 100%, and 92.9% at 1, 5, and 10 years, respectively) ($p = 0.039$, tested by log-rank test). Similarly, compared with the patients receiving HD, those who received KT had a trend of better survival outcome after correcting for sex and age at renal replacement therapy in the multiple Cox regression analysis. The unadjusted hazard ratio for mortality was 0.21 (95% CI: 0.05–1.02; $p = 0.053$), while the adjusted hazard ratio was 0.21 (95% CI: 0.04–1.05; $p = 0.058$) (Table 3).

In the HD group, 6 patients died of infection, 1 died due to SLE flare-up, and another succumbed to seizure. In the PD group, 1 patient died of infection and 1 patient died due to cardiovascular morbidity. Regarding the KT group, 1 died due to SLE flare-up and 1 patient died from malignancy.

Table 2 Adverse events during renal replacement therapy.

	HD (n = 42)	PD (n = 12)	KT (n = 40)	p Value
SLE flare-up	9 (21)	0 (0)	3 (8)	0.061
Fever	4	0	0	0.075
CNS lupus	2	0	2	0.736
Thrombocytopenia	1	0	1	0.861
Lupus nephritis	0	0	1	0.505
Arthralgia	1	0	0	0.535
Serositis	2	0	0	0.282
Infection	16 (38)	5 (42)	16 (40)	0.970
UTI	0	0	8	0.003
AVF infection	7	0	0	0.009
Peritonitis	2	4	1	0.001
Sepsis	5	0	0	0.038
Pneumonia	4	1	5	0.875
Herpes zoster	0	0	4	0.060
Cellulitis/ osteomyelitis	3	0	0	0.147
Sinusitis	0	0	2	0.252
Tuberculosis	0	0	1	0.505
Brain abscess	0	0	1	0.505
Cardiovascular morbidity	19 (45)	2 (17)	4 (10)	0.002
AVF dysfunction	15	1	1	<0.001
Aneurysm	2	0	2	0.736
Thrombosis	2	0	1	0.673
Arrhythmia	1	1	0	0.212
Hypertension crisis	2	0	0	0.282
Malignancy	3 (7)	1 (8)	2 (5)	0.885

Data are presented as patient number (%).

AVF = arteriovenous fistula; CNS = central nervous system; HD = hemodialysis; KT = kidney transplantation; PD = peritoneal dialysis; SLE = systemic lupus erythematosus; UTI = urinary tract infection.

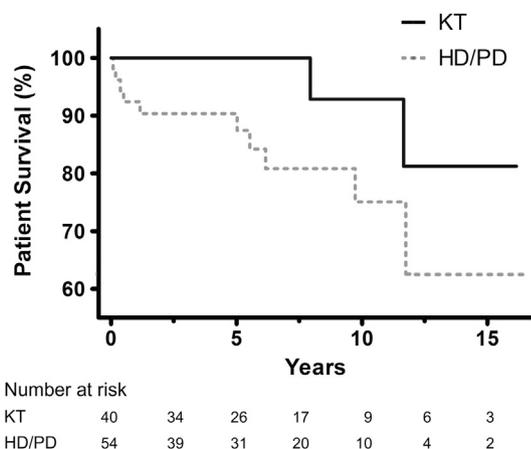


Figure 1. The survival of patients in the HD/PD group and in the KT group. HD = hemodialysis; KT = kidney transplantation; PD = peritoneal dialysis.

Compared with the patients receiving KT, those who received HD had an increasing trend of mortality from infection ($p = 0.026$) (Table 4).

The HD/PD technique survival (censored for dysfunction of AVF or PD tube) was 71.9% and 59.6% at 5 and 10 years in the HD/PD group, respectively. The graft survival (censored for loss of allograft) was 87.2% and 71.2% in the KT group, respectively.

Discussion

In this single medical center study, we compared the long-term outcomes and survival rates of SLE patients with ESRD caused by lupus nephritis who received three different modalities of renal replacement therapy, including hemodialysis, peritoneal dialysis, and kidney transplantation. The patients receiving hemodialysis had more cardiovascular complications, primarily AVF dysfunction. The incidences of other morbidities such as SLE flare-up, infection, and malignancy were not significantly different among groups receiving the three treatment modalities. However, infection problems differed among these groups. AVF infection and sepsis were more common in the HD group than in the KT group; the risk of peritonitis was higher in the PD group than in the HD and KT groups; UTI was more common in the KT group than in the HD group. Finally, cumulative survival rates were better in the KT

Table 4 Cause of death.

	HD (n = 42)	PD (n = 12)	KT (n = 40)	p Value
Infection	6	1	0	0.034
SLE flare-up	1	0	1	1.000
Seizure	1	0	0	1.000
Cardiovascular morbidity	0	1	0	0.128
Malignancy	0	0	1	0.553

Data are presented as patient number. HD = hemodialysis; KT = kidney transplantation; PD = peritoneal dialysis; SLE = systemic lupus erythematosus.

group than in both dialysis groups, and infection was the most common cause of mortality in the patients receiving hemodialysis. Therefore, kidney transplantation is the better choice of treatment.

In our study, the patients in the KT group developed ESRD at younger ages than the patients in the dialysis groups, but the ages at kidney transplantation were very similar to the ages at dialysis induction in the HD and PD groups, and the follow-up periods were not significantly different. One may presume that the KT group had a poorer clinical outcome due to the longer period of ESRD. However, our results showed that they had better survival rates and developed less morbidities (except for UTI) during the follow-up period. This showed that clinical outcome and quality of life were superior in recipients of kidney transplantation than in recipients of dialysis. Similar results have been reported by Kang et al.¹¹ A possible explanation was the use of immunosuppressants in the KT group. In our study, most of the patients were prescribed calcineurin inhibitors, mycophenolate mofetil, and prednisolone after kidney transplantation, while the patients receiving dialysis were given prednisolone only.

In this study, infection was the main complication of renal replacement therapy, and UTI was the most common complication of kidney transplantation. Previous studies have reported that UTI occurred in 30–60% of kidney transplant recipients during the first year after the procedure, accounting for approximately 40–50% of all infectious complications.^{12,13} Many risk factors were reported to influence the incidence of UTI, including age, female gender, original kidney disease and co-morbidities, use of cadaver grafts, surgical manipulation during transplantation, and the dosage and duration of

Table 3 Multiple Cox regression analysis of survival outcomes in the lupus patients receiving renal replacement therapy.

Variable	Unadjusted		Adjusted	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Male sex	4.57 (1.30–16.05)	0.018	4.99 (1.33–18.68)	0.017
Age at the beginning of RRT (years)	1.04 (0.99–1.09)	0.117	1.03 (0.98–1.08)	0.229
RRT type				
HD	Reference		Reference	
PD	0.74 (0.15–3.63)	0.711	0.94 (0.18–4.82)	0.940
KT	0.21 (0.05–1.02)	0.053	0.21 (0.04–1.05)	0.058

HD = hemodialysis; KT = kidney transplantation; PD = peritoneal dialysis; RRT = renal replacement therapy.

immunosuppressants.^{12–15} UTI after kidney transplantation was associated with increased mortality and graft failure; therefore, surveillance of UTI for the first 3 months after kidney transplantation is recommended to improve the quality of life of the recipient and also the functional outcome of the graft.^{16,17}

The disease activity of lupus patients with ESRD under renal replacement therapy has been extensively studied.^{1,7,8,18–20} In 1990, a retrospective study in lupus patients receiving HD and PD found that both groups had a similar decrease in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).²¹ A more recent retrospective study revealed a significant decrease in SLEDAI in lupus patients after kidney transplantation.⁷ The study of Kang et al. comparing different modalities of renal replacement therapy found that SLE flare-up was less severe in patients undergoing kidney transplantation than in patients receiving HD and PD.¹¹ In our study, the rate of SLE flare-up was similar in all three groups.

The recurrence of lupus nephritis after kidney transplantation is an important issue in patients with ESRD caused by SLE because it was associated with allograft loss, although it had no influence on patient survival.⁵ In the related literature, the variable ethnic composition of the patients and differences in renal biopsy guidelines may account for the wide variation in incidence (0–30%).^{7,22–25} In this study, only one of the 40 patients in the KT group (2.5%) developed recurrent lupus nephritis, which is compatible with the incidence in previous studies.

In this study, the incidence of malignancy was similar regardless of the modality of renal replacement therapy. Nevertheless, most of the patients were younger than 50 years old at the end of follow-up period. With the advancement of the treatment of ESRD secondary to lupus nephritis and as improvements in overall survival are achieved, the issue of malignancy and cardiovascular disease will become increasingly important and merit more study.

Previous studies showed that the cumulative survival rate in lupus patients who progressed to ESRD at 5 years was 83–92% in HD recipients, 53–80% in PD recipients, and 77–97% in KT recipients.^{7,8,10,22,26–29} In comparison, all of our patients in the KT group survived at 5 years. One possible explanation is the widespread use of mycophenolate mofetil, a novel immunomodulating drug.

Reviewing the literature, patient and graft survival after kidney transplantation in patients with ESRD caused by lupus nephritis have been studied extensively and shown to be similar to those in matched non-lupus patients.^{7–10} However, studies comparing the clinical outcomes of lupus recipients of dialysis with that of lupus recipients of kidney transplants were limited.^{1,30} The aim of these studies was to analyze survival rate or disease activity after three renal replacement therapies, but not other adverse events. In our study, not only survival outcome but also adverse events and cause of death were assessed. Regarding the clinical outcome, only one recent study showed that KT provided a lower complication rate than HD or PD among patients with ESRD caused by SLE.¹¹ Our study enrolled more patients than the above study. In addition, we used multiple Cox regression analysis to estimate mortality hazard ratios after adjustment for potential confounders including age and sex.

Our analysis is burdened by a number of limitations. First, due to the rarity of ESRD secondary to lupus nephritis, it is difficult to recruit a large sample of patients in a single-center study. Second, because few patients with ESRD caused by lupus nephritis received initial PD,³¹ we could not recruit a sufficient number of patients in PD group. However, compared with our study, previous studies have also achieved positive results with a similar or smaller sample size.^{1,11,21} Therefore, further studies could be conducted to overcome the selection bias due to small sample sizes. Third, there was a marked female predominance in lupus patients, especially in those who received PD. The gender difference was variable across published studies.^{1,8,11,31,32} Therefore, we used multiple Cox regression analysis that took the gender difference into account. Finally, despite many published studies have shown that the results after kidney transplantation were similar in lupus patients and non-lupus patients, one methodological limitation of the present study could be the lack of a non-SLE control.

In conclusion, this study demonstrated that lupus patients with ESRD who underwent kidney transplantation had better long-term outcomes and survival rates than those who received hemodialysis or peritoneal dialysis. This implies that kidney transplantation is the better choice of renal replacement therapy in the patients with ESRD caused by lupus nephritis.

Conflicts of interest

We have no potential financial or non-financial conflicts of interest.

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