International Archives of Medical Research 12:2 (2020) 16-24

ORIGINAL RESEARCH PAPER

Mortality Analysis of Patients with Lupus Nephritis

Geliş Tarihi: 21.10.2020, Kabul Tarihi: 05.12.2020

Mehmet Ali Balcı[1*], Enver YÜKSEL[1]

1. Department of Rheumatology, University of Health Sciences Gazi Yaşargil Training and Research Hospital, Diyarbakir-TURKEY; ORCID ID: 0000-0003-0597-7788

2. Department of Nephrology, University of Health Sciences Gazi Yaşargil Training and Research Hospital, Diyarbakir-TURKEY; ORCID ID: 0000-0003-0302-932X

Abstract

Lupus nephritis (LN), which is an important clinical finding of systemic lupus erythematosus (SLE), may lead to death if not treated. In our study, we aimed to investigate the causes of mortality, 5-year and 10-year survival rates, and standardized mortality ratios (SMR) of patients with LN. 73 LN patients were included in the study. Age, gender, diagnosis, treatment, laboratory and pathology data of these patients were retrospectively scanned and recorded.

63(86.3%) female and 10(13.7%) male LN patients were included in the study. The most prevalent clinical criteria detected in these patients were proteinuria 73(100%). During the follow-up period, death occurred in 4(5.5%) patients. The 5 and 10-year survival rate of the patients was calculated as 95.7% and 94.0% respectly. Cox regression analysis revealed that the prognosis of the disease was significantly more mortal in male patients compared to the female patients [p = 0.01, HR = 19.248]. On the other hand, SMR was determined as 5.52 in SLE patients with LN, which indicates a higher SMR compared to the general population.

Our study is the first LN mortality series study in Turkey. The mortality rates determined in our study were found to be comparable to the mortality rates reported in the literature. Male gender was determined as the risk factors associated with LN in terms of mortality. Hence, male LN patients should be followed up more closely.

Key Words: *Systemic lupus erythematosus, Lupus nephritis, Mortality*

Corresponding author: E-mail: abalci13@gmail.com

Introduction:

SLE is a chronic autoimmune disease of unknown cause that can affect almost any organ in the body. LN is detected in approximately 50 percent of SLE patients and is an important cause of morbidity and mortality[1]. In today's world, the survival time of LN patients has been significantly prolonged compared to the past due to factors such as better socio-economic conditions, early diagnosis, improvements in immunosuppressive and supportive treatments. Infections remain a major cause of mortality, whereas cardiovascular complications have been a major cause of late mortality in the event of longer patient survival[2-4].

Whether the mortality rate in patients with LN is higher compared to the mortality rate in the general population can be calculated by SMR[5]. It has been reported in the literature that the SMR of SLE patients without LN is 2.4 times higher than the general population, whereas the SMR of SLE patients with LN was 6.0 times higher than the general population[3-6]. The mortality rate in patients with SLE in our country has been studied[7], however there has been no study to date, in which the mortality in patients with LN in our country was investigated. Therefore, in our study, we aimed to investigate the causes of mortality, 5-year and 10-year survival rates, and SMR of patients with LN.

Material&Method:

73 patients that applied to University of Health Sciences Gazi Yaşargil Training and Research Hospital Rheumatology Outpatient Clinic during the period of 2010 to 2020 and who were diagnosed with LN as substantiated by biopsy were included in the study. Age, gender, diagnosis, treatment, laboratory and pathology data of these patients were retrospectively scanned and recorded. All patients were re-evaluated in terms of their SLE diagnosis using the 2019 EULAR (European League Against Rheumatism) / ACR (American College of Rheumatology) classification criteria and their diagnoses were confirmed[8]. The SLEDAI and ACR Damage Index of the patients were calculated. Vital records (birth and death) of patients were obtained from the Turkish Statistical Institute[9,10]. Statistical analyses were performed using the SPSS V21.0 (SPSS Inc., Chicago, IL) software. Chi-square test was used to compare the categorical data, whereas Fisher's exact test was also used in cases deemed necessary. Cumulative survival curves were created using the Kaplan-Meier method and the difference between curves was tested using the log-rank test. Univariate and multivariate Cox regression analysis was used to determine the independent factors affecting survival. Values of $p<0.05$ have been considered statistically significant. The ethics committee approval

required to conduct the study has been obtained from University of Health Sciences Gazi Yaşargil Training and Research Hospital.

Results:

A total of 73 SLE patients, 63 (86.3%) of whom were female and 10 (13.7%) of whom were male, were included in our study. The mean age of the patients was calculated as 30 ± 10.7 years. The most prevalent clinical criteria detected in these patients were proteinuria, which was detected in 73 (100%) patients, arthritis, which was detected in 56 (76.7%) patients, and photosensitivity, which was detected in 49 (67.1%) patients. On the other hand, the most prevalent immunological criteria detected in these patients were ANA (antinuclear antibody) positivity, which was detected in 72 (98.6%) patients, anti-ds(double stranded)DNA positivity, which was detected in 55 (75.3%) patients, and low complement C3 (component-3), which was detected in 44 (60.3%) patients. Detailed data are given in **Table 1**. The pathology results of our study indicated that 35 (47.9%) patients had class IV LN, 16 (21.9%) patients had class III LN, 10 (13.7%) patients had class V LN, 8 (11.0%) patients had class II LN, 3 (4.1%) patients had class I LN, and 1 (1.4%) patient had class VI LN.

Table 1: Basic clinical and laboratory characteristics of SLE patients

Age, male/female/general, (mean ±sd)	30.7±11.5 / 28±8.7/30±10.7
Female, n(%)/Male, n(%)	63 (86.3) / 10 (13.7)
Duration of illness (month)	138.1±126.4
Death, n(%)	4 (5.5)
Arthritis, n(%)	56 (76.7)
Photosensitivity, n(%)	49 (67.1)
Raynaud, n(%)	20 (27.4)
Malar rash, n(%)	30 (41.1)
Diskoid rash, n(%)	8 (11.0)
Oral aphthae, n(%)	32 (42.5)
Pleurit, n(%)	11 (15.1)
Pericarditis, n(%)	7 (9.6)
Alopecia, n(%)	11 (15.1)
Neurological involvement, n(%)	6 (8.2)
Proteinuria (>500 mg/day) , n(%)	73 (100)
Active sediment,n(%)	49 (67.1)
Hemodialysis, n(%)	3 (4.1)
Leukopenia, n(%)	32 (43.8)
Lymphopenia, n(%)	28 (38.4)
Hemolytic anemia, n(%)	7 (9.6)
Thrombocytopenia, n(%)	10 (13.7)
ANA, n(%)	72 (98.6)
Anti-dsDNA, n(%)	55 (75.3)
Anti-ro, n(%)	18 (24.7)

Anti-sm, n(%)	10 (13.7)
Low C3, n(%)	44 (60.3)
Low C4, n(%)	39 (53.4)
Direct coombs, n(%)	17 (23.3)
SLICC/ACR Damage İndeks, mead±sd	1.16±1.45
SLEDAI, mean±sd	17.63±8.52

n: number, sd: standard deviation

In terms of comorbidity, it was determined that 15 (24.7%) patients had hypertension and 5 (6.8%) patients had diabetes; whereas in terms of medication, it was determined that 72 (98.6%) patients were using hydroxychloroquine, 70 (95.9%) patients were using steroid, 47 (64.4%) patients were using azathiopurine and cyclophosphomide. Detailed data are given in **Table 2**.

Table 2: Risk factors and use of medication in patients with systemic lupus erythematosus (SLE)

Hypertension, n(%)	15 (24.7)
Diabetes, n(%)	5 (6.8)
Hypothyroidism, n(%)	2 (2.7)
Hyperlipidemia, n(%)	4 (5.5)
Steroid, n(%)	70 (95.9)
Hydroxychloroquine, n(%)	72 (98.6)
Azathiopurine, n(%)	47 (64.4)
Mycophenolate Mofetil, n(%)	33 (45.2)
Cyclophosphomide, n(%)	47 (64.4)
Methotrexate, n(%)	3 (4.1)
Cyclosporine, n(%)	6 (8.2)
Rituximab, n(%)	12 (16.4)
Acetylsalicylic acid, n(%)	20 (27.4)
Anticoagulant, n(%)	3 (4.1)

The mean disease duration of the patients was calculated as 138.1 ± 126.4/month. Death occurred in 4 (3 male, 1 female) patients (5.5%) out of the 73 patients during the course of the disease. Considering the causes of death, it was determined that 1 patient died due to central nervous system involvement, 1 patient died due to heart failure, 1 patient died due to development of acute myeloid leukemia, and 1 patient died due to sepsis. The detailed clinical and laboratory characteristics of 4 patients who had died are given in **Table 3**. The 5-year survival rate of the patients was calculated as 95.7%, whereas the 10-year survival rate of the patients was calculated as 94.0% (**Figure 1**).

Table 3: Clinical and laboratory characteristics and causes of death of patients who had died

Age/ Gender	Duration of illness (months)	DM/HT	Lupus Nephritis Class	Neurological involvement	Hemolytic anemia	Thrombocytopenia	Pleurit / Pericarditis	Anti-dsDNA	Treatment	Cause of death	SLEDAI	SLICC/ACR Damage Index
37/F	64	-/-	4	+	-	+	+/-	+	Steroid, Hydroxychloroquine, Cyclosporine, Cyclophosphomide	cns involvement	26	4
31/M	5	-/-	2	-	+	-	+/+	-	Steroid, Hydroxychloroquine, Azathiopurine, Cyclophosphomide	Heart failure	12	1
26/M	26	-/-	3	-	-	-	-/+	-	Steroid, Hydroxychloroquine, Azathiopurine, Cyclophosphomide	AML	23	2
24/M	8	-/-	4	-	-	-	-/-	+	Steroid, Hydroxychloroquine, Mycophenolate Mofetil , Rituximab, Cyclophosphomide	Sepsis	18	1

CNS: Central nervous system, AML: Acute myeloid leukemia

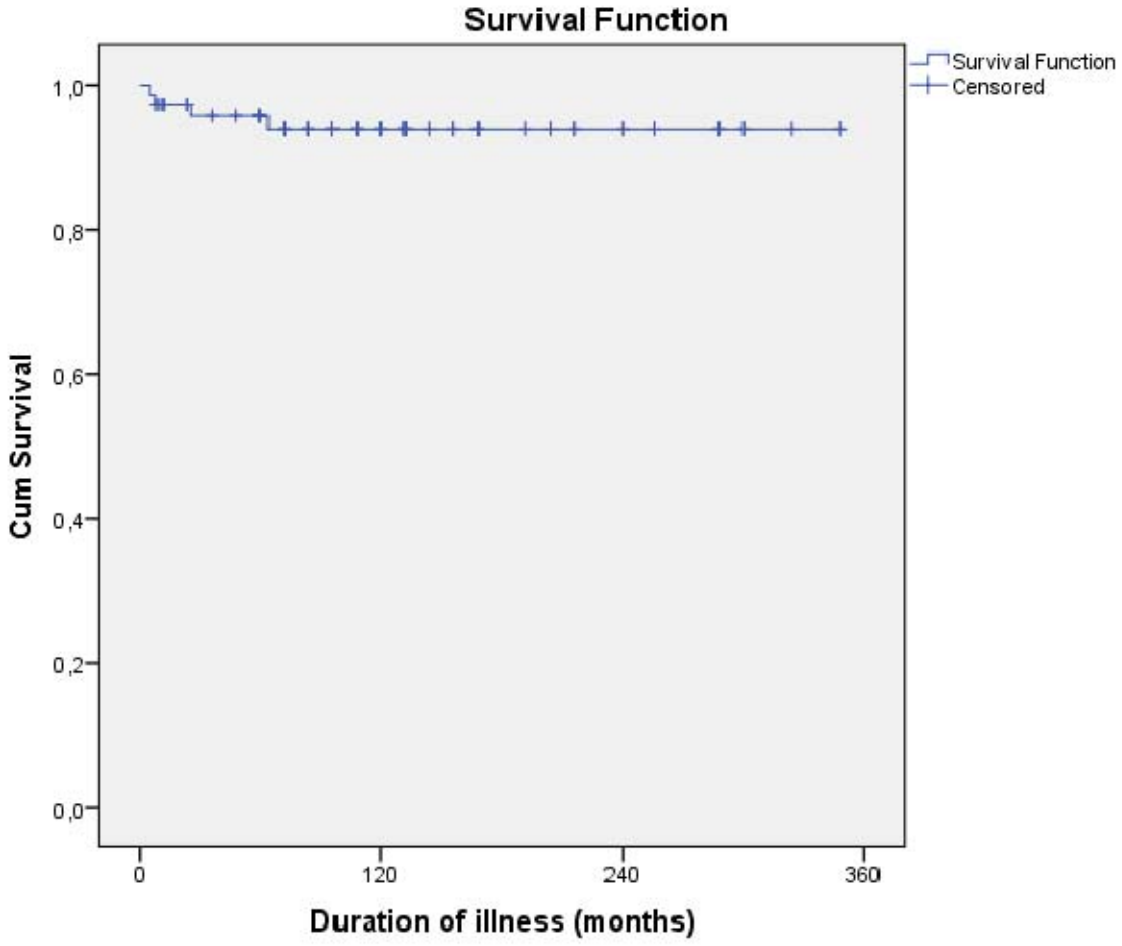

Figure 1: Survival analysis in patients with LN

Cox regression analysis revealed that the prognosis of the disease was significantly more mortal in male patients compared to the female patients [p = 0.01, HR (Hazard Ratio) = 19.248], and in patients with pericarditis compared to the patients without pericarditis (p = 0.02, HR = 9.822). Interestingly, deaths were statistically significantly higher in those without photosensitivity (p = 0.01, HR = 0.004). Univariate Cox regression analysis did not reveal any significant difference between the survivors and the deceased in terms of LN classes and other clinical, laboratory and treatment characteristics. In multivariate cox regression analysis, only gender was found to have a significant effect on mortality (HR: 13.856, p= 0.02). Detailed data are given in **Table 4**.

Table 4: Univariate and Multivariate Cox regression analysis of mortality and clinical parameters in patients with lupus nephritis

	Univariate analysis		Multivariate analysis	
Risk Factor	HR (95% CI)	p	HR (95% CI)	p
Age	0.992 (0.904-1.088)	>0.5		
Gender	19.248 (1.999-185.334)	0.01	13.856 (1.347-142.572)	0.02
Diabetes	0.045 (0.000-1297014.287)	>0.5		
Hypertension	0.032 (0.000-558.735)	>0.5		
Oral aphthae	0.018 (0.000-61.007)	>0.5		
Malar rash	0.021 (0.000-77.419)	>0.5		
Arthritis	0.800 (0.083-7.7705)	>0.5		
Lymphopenia	0.472 (0.049-4.562)	>0.5		
Hemolytic anemia	3.165 (0.329-30.492)	>0.5		
Thrombocytopenia	1.844 (0.191-17.792)	>0.5		
Pericadial effusion	9.822 (1.374-70.233)	0.02	0.237 (0.028-1.997)	0.18
Photosensitivity	0.004 (0.004-81.817)	0.01	204158.960 (0.000-2.181E+180)	0.95
SLEDAI	1.016 (0.908-1.137)	>0.5		
SLICC/ACR Damage Index	1.268 (0.767-2.095)	>0.5		

HR: Hazard Ratio, CI: 95% Confident Interval

The survival rate of the general population has been 95.72% during the period between 2008 and 2017 according to the statistics of the Turkish Statistical Institution[9,10], whereas the survival rate of patients with LN in our cohort was determined as 94.0%. On the other hand, SMR was determined as 5.52 in SLE patients with LN, which indicates a higher SMR compared to the general population.

Discussion:

LN is a serious cause of morbidity and mortality in patients with SLE. Nonetheless, today, the 5-year survival rate associated with LN today is 99.3%[4], which indicates a substantial improvement compared to the 5-year survival rate associated with LN, which was 44% in the 1950s[11]. Many factors have contributed to the said improvement observed in the survival rate associated with LN, including early diagnosis, easy access to healthcare, advances in immunosuppression therapy, dialysis, transplantation, and treatment of comorbidities.

Our literature review revealed that there has been a few studies, in which mortality rates associated with LN were studied; however none of these studies included any results from Turkey. Therefore, our cohort study is the first study, in which the mortality of patients with LN in Turkey was studied. In our study, the 5-year survival rate of the patients was calculated as 95.7%, whereas the 10-year survival rate of the patients was calculated as 94.0%. In comparison, in the literature, the 5-year survival rates were reported within the range of 44% to 99.3%[3,4,11,12] and the 10-year

survival rates were reported within the range of 88% to 93%[3,4,12] which are similar to the results of our study.

In our study, SMR was determined as 5.52 in SLE patients with LN, which indicates a higher SMR compared to the general population. In comparison, the SMRs of patients with LN have been reported as 6[3] and 6.8[13] in the literature. Despite the fact that life expectancy of patients with LN has increased in recent years[4], the mortality rate in patients with LN remains still high compared to the mortality rate in general population.

Death occurred in 4 of the patients included in our study. Their causes of death were determined as cardiovascular complications, malignancy, neurological involvement and infection. Similar causes of death have been reported in patients with LN in the literature[4,14]. Ethnic origins and socio-economic status of the patients are among the factors that have to be taken into consideration in assessing the SLE-related mortality. In our cohort, however, all patients were from the same ethnic background, thus we did not need to take ethnic origins of the patients into account when assessing the SLE-related mortality. On the other hand, we could not evaluate the SLE-related mortality in terms of the socio-economic status of the patients, since a complete set of relevant data were not available.

In our study, male gender, pericarditis and lack of photosensitivity were determined as the risk factors associated with LN in terms of mortality. However, in the multivariate cox regression analysis, only gender was found to have a significant effect on mortality (HR: 13.856, $p = 0.02$). In comparison, in the literature, male gender has been associated with twice as higher mortality rates in patients with LN compared to the female gender[15,16]. However, we did not come across any study in the literature, in which the effect of pericarditis and lack of photosensitivity on LN-related mortality has been studied.

Although it is known that high disease activity index is an indicator of mortality in patients with LN[17] in our cohort, univariate Cox regression analysis did not reveal any increase in LN-related mortality, neither in patients with class IV (diffuse proliferative) LN nor in those with high SLEDAI scores. Therefore, we have concluded that active inflammatory and proliferative kidney changes maintain their importance in the selection of treatment and do not cause an increase in LN-related mortality in the long-term.

Conclusion: Our study is the first LN mortality series study in Turkey. The mortality rates determined in our study were found to be comparable to the mortality rates reported in the literature. Male gender was determined as the risk factors associated with LN in terms of mortality. Hence, male LN patients should be followed up more closely.

References

1. Danila MI, Pons-Estel GJ, Zhang J, Vila LM, Reveille JD, Alarcon GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford). 2009;48: 542-5.

2. Ippolito A, Petri M. An update on mortality in systemic lupus erythematosus. Clin Exp Rheumatol. 2008;26:S72-9.

3. 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.

4. Ichinose K, Kitamura M, Sato S et al. Factors predictive of long-term mortality in lupus nephritis: a multicenter retrospective study of a Japanese cohort. Lupus. 2019;28:295-303.

5. Yavuz Ş. Sistemik Lupus Eritematozus ve Mortalite. Türkiye Klinikleri. 2018:102-4.

6. Bernatsky S, Boivin JF, Joseph L et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54:2550-7.

7. Pamuk ON, Akbay FG, Donmez S, Yilmaz N, Calayir GB, Yavuz S. The clinical manifestations and survival of systemic lupus erythematosus patients in Turkey: report from two centers. Lupus. 2013;22:1416-24.

8. Aringer M, Costenbader K, Daikh D et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019;71:1400-12.

9. Ölüm Nedeni İstatistikleri [https://data.tuik.gov.tr/Bulten/Index?p=Olum-ve-Olum-Nedeni-Istatistikleri-2019-33710]

10. Adrese Dayalı Nüfus Kayıt Sistemi Sonuçları [https://tuikweb.tuik.gov.tr/PreHaberBultenleri.do;jsessionid=pT27fntc1TPshcphN2cqf9XGPbtpYRp8R30DNpCscjzfrtN0skQ2!-608163093?id=30709]

11. Cameron JS. Lupus nephritis. J Am Soc Nephrol. 1999;10:413-24.

12. Teh CL, Phui VE, Ling GR, Ngu LS, Wan SA, Tan CH. Causes and predictors of mortality in biopsy-proven lupus nephritis: the Sarawak experience. Clin Kidney J. 2018;11:56-61.

13. 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.

14. Bultink IEM, de Vries F, van Vollenhoven RF, Lalmohamed A. Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. Rheumatology (Oxford). 2020.

15. Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine (Baltimore). 2006;85:147-56.

16. Pattanaik SS, Muhammed H, Chatterjee R et al. In-hospital mortality and its predictors in a cohort of SLE from Northern India. Lupus. 2020;29:1971-7.

17. Momtaz M, Fayed A, Wadie M et al. Retrospective analysis of nephritis response and renal outcome in a cohort of 928 Egyptian lupus nephritis patients: a university hospital experience. Lupus. 2017;26:1564-70.