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ORIGINAL ARTICLE

Survival Analysis of Turkish Patients With Systemic Lupus Erythematosus: Older Age at Diagnosis Affects Mortality

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ABSTRACT

Objectives: This study aims to determine the rate, causes, and risk factors of mortality in Turkish systemic lupus erythematosus (SLE) patients and whether age at diagnosis has an effect on mortality or not.

Patients and methods: We retrospectively analyzed the data from 221 patients (10 males, 211 females; mean age 41.5±13.5 years; range 18 to 74 years) who were followed-up due to the diagnosis of SLE in our department between January 1998 and March 2016. Detailed clinical findings, organ involvements, autoantibodies, and complement levels of the patients were recorded.

Results: Of the entire group, 19 patients (8.6%) died. Mortality incidence rate was 1.05/100 patient-years. Most frequent causes of death were infections, ischemic cardiovascular and cerebrovascular diseases. Through univariate analysis, older age at diagnosis and a short duration of follow-up were identified as the only factors with an influence on mortality (p=0.004 and p=0.002, respectively). Beyond the mentioned factors, organ involvements in SLE, autoantibodies or antiphospholipid antibody syndrome were not found to have a relationship with mortality. Further analysis conducted on late-onset, defined as the patient age of 50 or above at diagnosis, versus adult-onset, defined as the diagnosis at an age of younger than 50 years, revealed a remarkably shorter survival in patients diagnosed after age of 50 (p=0.003). Cumulative five-year, 10-year, and 15-year survivals of patients were 91.9%, 90%, and 88.2%, respectively.

Conclusion: We identified older age at diagnosis as an effective factor on mortality. SLE patients who are diagnosed at an older age should be more closely and meticulously followed-up than those diagnosed earlier in terms of their mortality risk.

Keywords: Mortality; systemic lupus erythematosus, survey; Turkey.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease severely affecting body organs, which may get damaged during the course of the disease. Mortality is increased in SLE when compared to the general population.[1] Survival rates vary by the geographic regions.[2] In addition to the disease-related factors which may influence the mortality, medications used during the treatment have also been investigated for their effects on mortality.[3-5] Among the patients who are followed-up due to SLE, most predominant causes of death at the early period are infection and serious organ involvement of SLE. Existence of renal involvement, particularly, is one of the findings leading to poor prognosis.[2,5] Recently, data have been accumulating on the negative effect of late disease onset on survival.[5,6] To our knowledge, there is only one Turkish study on survival in SLE in which age at diagnosis was not determined as an effective factor on mortality.[4]

In this study, we aimed to determine the rate, causes, and risk factors of mortality in Turkish SLE patients and whether age at diagnosis has an effect on mortality or not.

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PATIENTS AND METHODS

This study was carried out with a SLE cohort composed of 221 patients (10 males, 211 females; mean age 41.5±13.5 years; range 18 to 74 years) who were admitted to the Rheumatology Department of Eskişehir Osmangazi University Hospital between January 1998 and March 2016 as they were diagnosed with SLE based on the 1997 revised American College of Rheumatology criteria.[7] Patients were assessed every two-four weeks if they suffered serious organ involvements and every one-three months in the event of no serious involvement. Patients who had visited our center for at least two times were enrolled into the study. Demographic findings at the time of diagnosis, clinical findings, organ involvements, results for serological parameters (anti-nuclear antibody, anti-double stranded deoxyribonucleic acid [anti-dsDNA], anti-Smith antibody, antiribonucleoprotein [anti-RNP], anti-Sjögrens syndrome-A [Ro], anti-Sjögrens syndrome-B [La]), complement levels, hematological values, urine analysis, erythrocyte sedimentation rate and C-reactive protein levels at the time of diagnosis, and the medications used during the entire term of follow-up (corticosteroid, hydroxycloroquine, cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, warfarin) were recorded as deducted from the patient files and electronic registry system. Moreover, their cumulative organ involvements and existence of cumulative antiphospholipid antibodies (anticardiolipin immunoglobulins M and G, lupus anticoagulant) and antiphospholipid syndrome (according to 2006 Sapporo criteria) were recorded.[8] Follow-up period was accepted as the time elapsed from diagnosis to either last follow-up or death. In the event of a death occurring at the hospital, relevant data were obtained via hospital file record system or the hospital electronic registry system. Patients lost to follow-up were checked by calling their relatives in order to determine whether they were alive or not. Causes of death were noted down for deceased patients. Organ involvements were assessed based on the American College of Rheumatology classification criteria.[7]

Anti-nuclear antibody testing was carried out by indirect immunofluorescence method, accepting >1/160 as positive. Immunoblotting assay was used to detect anti-Smith antibody, anti-RNP, anti-Ro, and anti-La antibodies. Anti-dsDNA, and anticardiolipin immunoglobulins M and G were tested by enzyme-linked immunosorbent assay method and lupus anticoagulant was screened by functional coagulation tests. Likewise, complement levels were measured using nephelometric method. Anti-dsDNA and complement levels were determined at the time of diagnosis, of a suspected exacerbation, and in every six months if the patient had no problems.

The study protocol was approved by the Eskişehir Osmangazi University Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

IBM SPSS for Windows version 22.0 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis of the results. Within a confidence interval of 95%, the value $p<0.05$ was accepted as statistically significant. Measurement variables were presented as mean ± standard deviation. Normality assumptions were tested by Shapiro Wilk test. Parametric tests were carried out with normally distributed data, and non-parametric tests were performed if with data were not normally distributed. Abnormally distributed data were presented as median and 25-75th percentile. Independent samples t-test and Mann-Whitney U test were used in the comparison of two independent groups. Chi-square test was employed to conduct analyses of cross tables. Kaplan-Meier method was applied to analyze 5-, 10-, and 15-year survivals of the patients both cumulatively and by diagnosis before or after 50 years of age. Univariate analysis using independent sample t-test was performed in order to assess intergroup median variances. Risk factors for survival were studied by both binary logistic regression and Cox proportional hazards regression models.

RESULTS

Average duration of disease was 8.1±6.2 years (range 1-33 years) (Table 1). Most common complaints at admission were malar rash and joint pain. Cumulatively, most common complaints

Table 1. Clinical characteristics of systemic lupus erythematosus patients

	n	%	Mean±SD	Range
Age (years)			41.5±13.5	18-74
Gender				
Female	211	95.5		
Age at the diagnosis of SLE (years)			32.5±13.1	10-70
Disease duration (years)			8.1±6.2	1-33
Follow-up period (years)			6.97±5.3	1-31
Mortality rate	19	8.6		
Cumulative drug using				
Hydroxychloroquine	215	97.3		
Corticosteroid	156	70.6		
Azathioprine	109	49.3		
Cyclophosphamide	48	21.7		
Mycophenolat-mofetil	20	9		
Methotrexate	16	7.2		
Acetylsalicylic acid	56	25		
Warfarin	37	16.7		

SD: Standard deviation; SLE: Systemic lupus erythematosus.

of the cohort were malar rash, photosensitivity, and articular involvement. SLE-associated antiphospholipid syndrome (APS) was detected in 57 patients (25.8%). Of the entire group, 70.6% had used steroids. Most widely received immunosuppressive agent was azathioprine. Serological assays were positive for anti-nuclear antibody in 99.5% and for anti-dsDNA in 86.4% of patients. Other autoantibodies were measured positive at the following proportions: anti-Smith antibody in 21 patients (9.5%), anti-Ro in 31 patients (14%), anti-La in 20 patients (9%), and RNP in 24 patients (10.8%).

A total of 25 patients were lost to follow-up. Electronic registry system revealed out that 19 (8.6%) out of 25 patients had died at various departments of our hospital, while four were still followed-up in different departments. Of the remaining patients, relatives of two patients who had informed us that they were being followed-up in other centers were called to check. Mortality incidence rate was 1.05/100 patient-years (95% confidence interval 0.67-1.65). Of the deceased patients, 18 (94.7%) were females, median age of disease onset was 41 years (range 26-54), median age of death was 43 years (range 33-60), and median duration of disease until death was four years (range 1-5). The age at the time of diagnosis was significantly higher in deceased patients when compared to that of alive patients (p=0.008). In parallel, duration of disease and follow-up were shorter in deceased group (p=0.004 and p=0.002, respectively). Comparable proportions of individuals were positive for antibodies in deceased and alive group. Moreover, no difference was detected in terms of anticardiolipin antibodies, lupus anticoagulant, and APS (Table 2). Most frequent causes of death were infections, ischemic cardiac disorders, and ischemic cerebrovascular event. Only one patient died due to malignancy (bronchial carcinoma).

In the univariate analysis conducted to figure out the determinants of mortality, older age at the time of SLE diagnosis and shorter follow-up term were determined to be correlated with survival (p=0.008 and p=0.002, respectively). Beyond them, clinical findings of SLE, organ involvements including renal involvement, laboratory findings, presence of autoantibodies, decreased complement levels, and medication use were not found to have a relationship with survival. When we applied univariate analysis, age at diagnosis and duration of follow-up were the only variables found out to have a correlation with mortality. On the other hand, in addition to age at diagnosis and duration of follow-up, renal involvement, sex, serositis, APS existence, reduced complement level, and use of medication were assessed using binary logistic regression. Similarly, only age at diagnosis and duration of follow-up were determined as the variables with the major influence (Table 3). However, risk factors were not determined with Cox regression model.

Table 2. Main clinical and laboratory findings of systemic lupus erythematosus patients

	Deceased patients				Living patients				
	n	%	Median	25th and 75th percentile	n	%	Median	25th and 75th percentile	*p*
Age (years)			43	33-60			40	31-51	0.354
Gender									
Female			18	94.7			193	95.5	0.601
Age at the diagnosis of systemic lupus erythematosus (years)			41	26-54			30	21-40	0.008
Disease duration (years)			4	1-5			7	3-12	0.004
Follow-up period (years)			3	1-5			6	3-11	0.002
Organ involvements									
Malar rash	7	36.8			67	33.2			0.944
Discoid rash	2	10.5			11	5.4			0.309
Alopecia	1	5.3			15	7.4			>0.05
Oral ulcer	1	5.3			33	16.3			0.321
Joint involvement	5	26.3			39	19.3			0.546
Serositis									
Pericarditis	0	0			12	5.9			0.606
Pleuritis	2	10.5			9	4.5			0.242
Renal involvement	4	21.1			51	25.2			0.789
Neuropsychiatric involvement	1	5.2			19	9.4			>0.05
Fever	1	5.3			9	4.5			0.601
Antiphospholipid syndrome	5	26.3			52	25.7			>0.05
Thrombocytopenia	3	15.7			35	17.3			>0.05
Autoimmune hemolytic anemia	5	26.3			31	15.3			0.374
Leukopenia	8	42.1			53	26.2			0.178
Thrombosis	5	26.3			33	16.3			0.335
Hemoglobin levels at diagnosis (mg/dL)			11	9.7-12			11.75	10.28-12.70	0.130
Leucocyte levels at diagnosis (mm^3)			5000	3110-6800			5400	4000-7000	0.394
Absolute lymphocyte count levels at diagnosis (mm^3)			1000	690-1400			1200	875-1500	0.316
Absolute neutrophil count levels at diagnosis (mm^3)			3500	1900-4500			3350	2400-4500	0.516
Platelet levels at diagnosis (mm^3)			198000	117000-278000			226000	149000-283000	0.707
C-reactive protein levels at diagnosis (mg/dL)			0.49	0.14-1.25			0.32	0.19-0.68	0.216
Erythrocyte sedimentation rate levels at diagnosis (mm/hour)			45	31-87			43	18-73	0.144
C3 hypocomplementemia at diagnosis	10	52.6			99	49			0.951
C4 hypocomplementemia at diagnosis	9	47.4			96	47.5			>0.05
Antinuclear antibody positivity	19	100			201	99.5			>0.05
Anti-double stranded-deoxyribonucleic acid positivity	19	100			172	85.1			0.083
Smith antibody positivity	0	0			21	10.4			0.228
Anti-Sjögrens syndrome-A (Ro) positivity	1	5.3			30	14.9			0.486
Anti-Sjögrens syndrome-B (La) positivity	0	0			20	9.9			0.230
Anti-ribonucleoprotein positivity	0	0			24	11.9			0.237
Lupus anticoagulant positivity	1	5.3			42	20.8			0.133
Anticardiolipin-immunoglobulin G positivity	4	21.1			30	14.9			0.504
Anticardiolipin-immunoglobulin M positivity	1	5.3			12	5.9			>0.05

Table 3. Independent risk factors for mortality*

	OR	Lower CI	Upper CI	*p*
Age at the time of SLE diagnosis	1.04	1.01	1.08	0.008
Follow-up period	1.23	1.06	14.37	0.006

* Binary logistic regression; SLE: Systemic lupus erythematosus; OR: Odds ratio; CI: Confidence interval.

Cumulative five-year, 10-year, and 15-year survivals of patients were 91.9%, 90%, and 88.2%, respectively. A separate analysis conducted on the patients based on whether they were diagnosed before or after 50 years of age showed a remarkably shorter survival in patients diagnosed after age of 50 compared to patients diagnosed before age of 50 (p=0.003, Figure 1). In patients diagnosed before 50, five-year, 10-year, and 15-year survivals were 94.8%, 92.85%, and 92.85%, respectively, while corresponding survivals were 65.9%, 65.9%, and 52.7% in patients diagnosed after 50 years of age.

DISCUSSION

Age of disease onset, lifespans, and causes of death in our cohort were similar to other studies.[3,5,9] In the review by Kasitanon et al.,[3] death rate ranges between 2.8 to 38.6%. We have calculated mortality rate as 8.6% and mortality incidence rate as 1.05/100 patient-years in our cohort. Risk of death is two to five-fold increased in SLE compared to the usual population.[2] Mortality rates and survival terms differ by region. In a US cohort, 5- and 10-year survivals in patients who were diagnosed prior to versus subsequent to the age of 50 were 99.5% and 94.9% versus 97.8% and 89.5%, respectively.[5] In a review of studies conducted in USA and Europe, five-year survival ranged from 78 to 99.5%, 10-year survival ranged from 74 to 93.7% while 15-year survival was found to vary in a range of 60 to 91.6%.[2] The study carried out by Pamuk et al.,[4] the only study on mortality of SLE in Turkey, states 5-, 10-, and 15-year survivals as 96%, 92%, and 88.8%, respectively. In a similar manner to the study from Turkey and other studies in the literature, overall five-year, 10-year, and 15-year survivals of patients in our cohort were 91.9%, 90%, and 88.2%, respectively.

Cardiovascular diseases, infections, and disease activation are most common reasons of death among SLE patients. Usually, deaths occurring in the first years of disease are due to disease activation or infections induced by immunosuppressive treatment.[2,5] Standardized mortality ratios of 5, 1.7, and 0.8 were calculated for infections, cardiovascular diseases, and malignancy, respectively.[1] SLE-related deaths are more frequent among early diagnosed patients whereas deaths associated with infections and cardiovascular diseases were documented to be higher in late diagnosed patients.[5] In almost half of the patients, infection was the cause of death. Remaining half had died as a result of ischemic cardiovascular or ischemic cerebrovascular diseases. Activation of disease constitutes another cause of death in SLE patients. In the Chinese study by Wang et al.,[10] renal involvement accompanied by lupus encephalopathy held fourth place in their list of primary causes of death. Pamuk et al.[4] have stated most common causes of death as ischemic cardiac disease, chronic renal failure, and sepsis.

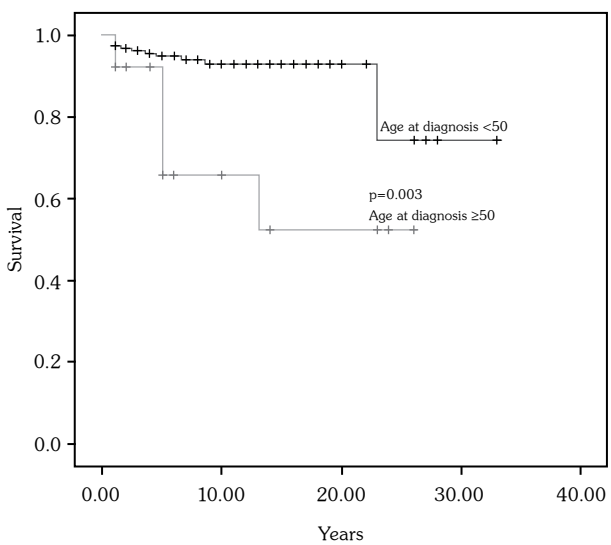

Figure 1. Survival by age of systemic lupus erythematosus diagnosis (Kaplan-Meier method).

Except for the above mentioned causes, lung cancer and lymphoma are other causes of death.[1] In our patients, most frequent causes of death were infections, and ischemic cardiovascular and cerebrovascular diseases. Only one of our patients had died due to bronchial carcinoma.

In search for the possible predictive factors for mortality in SLE patients, correlation with clinical findings in addition to sex, age of disease onset, race, education status, renal failure, central nervous system involvement, hemolytic anemia, thrombocytopenia, autoantibodies, complement levels, disease activity score, and disease damage score have been investigated.[3] The effect APS may exert on mortality, however, has been more rarely investigated.[11,12]

There are studies which have associated survival with the age at the diagnosis of SLE.[3,5,11-13] Being diagnosed after the age of 50 years has been associated with poor survival.[3] Ruiz-Irastorza et al.[11] have identified older age at the time of diagnosis as an independent risk factor for mortality. In another study in an attempt to minimize the effect of age on mortality, an age-matched control group was included, and, in conclusion, death risk in late-onset SLE patients was detected to be higher than that in adult-onset SLE patients.[13] The study of Merola et al.,[5] likewise, pointed out advanced age at the diagnosis as a predictor of decreasing 10-year survival, in particular.[5] In the study of Bernatsky et al.,[1] short disease term (<1 year) has increased standardized mortality ratio 5.4 times (95% confidence interval 4.7-6.3). In our study, older age at diagnosis was, similarly, detected as a predictor factor for mortality. We re-assessed the patients based on whether they were diagnosed before or after the age of 50 years. We have determined a shorter survival in patients who were diagnosed after turning 50 compared to those diagnosed earlier. Furthermore, a shorter period of follow-up was correlated with mortality.

Sex effect on mortality is explained by contradictory findings.[3-5,10] Several studies have associated male sex with poor diagnosis.[3-5] In the study of Bernatsky et al.[1] involving 23 sites, on the contrary, female sex was found to cause a 2.5-fold increased standardized mortality ratio (95% confidence interval 2.3-2.7). Dissimilar to named studies, we did not identify any relationship of sex with mortality.

There have been studies investigating the correlation of almost all clinical findings and symptoms of SLE with survival. In most of them, renal failure has been highlighted as a predictor of death.[3-5,9,11] In addition, there are studies which indicate another finding of disease, namely, presence of autoimmune hemolytic anemia as a risk factor for mortality.[3,4] Moreover, presence of serositis and thrombocytopenia were also indicated as independent risk factors in terms of prognosis.[4] High disease activity during the initial years of the disease, as scored by Systemic Lupus Erythematosus Disease Activity Index, was also proposed as a prognostic indicator.[3,4] Nonetheless, none of the clinical findings or organ involvements were found to be associated with survival in our study.

In a majority of the studies, autoantibodies (anti-dsDNA, anti-SS-A, lupus anticoagulant, Smith antibody, RNP) were not found to be correlated with mortality.[3,4,9] In the study by Kasitanon et al.,[3] existence of low complement C3 or complement C4 levels during the first year after diagnosis was associated to poor survival. Dissimilar to their study, we did not identify any correlation of autoantibodies or reduced complements with mortality.

Number of studies on the effect of APS on mortality in SLE is scant.[11,12] Some studies have investigated the influence on mortality of the anticardiolipins and lupus anticoagulants.[3,11] In a study comparing patients with SLE-associated APS to those with primary APS, no difference was determined between two groups regarding mortality incidence.[14] Kasitanon et al.[3] have not detected any correlation of lupus anticoagulants or anticardiolipin antibodies with survival. However, the study of Ruiz-Irastorza et al.[11] advocates APS as an essential independent risk factor for mortality. Additionally, Drenkard et al.[12] have found a correlation between presence of APS (ie. arterial occlusion related to antiphospholipid antibodies, hemolytic anemia and thrombocytopenia) and shortened lifespan. Out of 19 deceased patients in our study, five had APS co-existence. The cause of death in the patients with APS was acute myocardial infarction and cerebrovascular event, each of them gave rise to one death. However,

neither presence of APS nor antiphospholipid antibodies have been detected to have a correlation with mortality in our cohort.

It is challenging to identify the factors with an impact on mortality in SLE patients, as in addition to the peculiarities of the disease, immunosuppressive agents in use may have confounder effects. Lifespans have increased especially with the control on the disease achieved through the usage of steroids and immunosuppressive agents. On the other hand, infections which may arise in relation to the use of these agents may increase the mortality. Although in their evaluation of the correlation between medication and mortality in SLE, the Turkish study by Pamuk et al.[4] have associated cyclophosphamide use for >6 months with a shorter lifespan, the US study by Merola et al.[5] did not find a correlation of drug (ie. steroid, azathioprine, mycophenolate mofetil, and cyclophosphamide) use and survival in their entire group, despite a higher use of medication in the adult-onset group (>50 years). In a similar manner, in our deceased and alive patient groups, we have figured out comparable use of steroids and other immunosuppressive agents, and we did not find a correlation of steroid or immunosuppressive agent usage with survival.

Besides all disease-related factors discussed above which may have an effect on SLE mortality, there are studies which point out socioeconomic status rather than ethnicity as an important factor on disease progression and mortality.[15,16] Our results which differ from the other study conducted in Turkey suggest that except for the ethnicity, several environmental factors probably including socioeconomic status or comorbid conditions might have played a role in mortality.[4] On the other hand, similar to our study, the studies available in the literature evaluating the effects on mortality or survival in SLE patients are mostly in retrospective design and only a few studies involve general population as a control group. To our knowledge, there is no study in the literature which has assessed a similar chronic disease like SLE as a control group. Similarly, we did not have a control group composed of general population or similar chronic disease like SLE. In the literature review, however, we have encountered a study evaluating the factors affecting the mortality in patients with primary Sjögren's syndrome, a chronic disease which might be considered to be similar with SLE. That study does not conclude age at diagnosis as a factor with an impact on mortality, but refers to the presence of cryoglobulinemic vasculitis as a risk factor. The same study identified a death ration of 6%, a majority of losses being due to lymphoma.[17] Compared to the SLE patients, causes of death in primary Sjögren's syndrome are apparently different. Taking all these into consideration, therefore, both disease-related factors and environmental factors can be argued as factors affecting mortality in SLE patients.

Our study is primarily limited by its retrospective design. Other limitations include the relatively small number of patients and unavailability of disease activity scores in our assessments.

In conclusion, in our SLE cohort, we identified older age at diagnosis as an effective factor on mortality. Besides, cumulative five-year and 10-year survivals of our patients were above 90%, and thus outstanding. In conclusion, SLE patients who were diagnosed at an older age should be more closely and meticulously followed than those diagnosed earlier in terms of their mortality risk.

Declaration of conflicting interests

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