Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2026.43255
J Turk Soc Rheumatol 2026;18(1):98-107

Twenty-year retrospective analysis of mortality risk factors in patients with systemic lupus erythematosus: A single-center cohort with variable individual follow-up

Sistemik lupus eritematozus hastalarında mortalite risk faktörlerinin 20 yıllık retrospektif analizi: Tek merkezli kohort ve hastalar arasında değişken bireysel izlem süreleri

Zeynel Abidin Akar[1], Dilan Yıldırım[2]

[1]*Dicle University Faculty of Medicine, Department of Physical Therapy and Rehabilitation, Division of Rheumatology, Diyarbakır, Türkiye*
[2]*Dicle University Faculty of Medicine, Department of Physical Therapy and Rehabilitation, Diyarbakır, Türkiye*

Abstract

Objective: Mortality in systemic lupus erythematosus (SLE) reflects a complex interplay between disease activity, organ involvement, and treatment-related complications. This study aimed to evaluate the impact of demographic, clinical, and laboratory parameters on survival and identify independent predictors of mortality in a tertiary hospital-based SLE cohort over a 20-year accrual period with variable individual follow-up durations.

Methods: We retrospectively analyzed 184 patients with SLE who fulfilled the American College of Rheumatology/The European Alliance of Associations for Rheumatology classification criteria and were followed at a tertiary university hospital between 2005 and 2025. Clinical manifestations, baseline laboratory parameters, and survival outcomes were recorded. Follow-up duration was expressed as median (interquartile range) due to a skewed distribution. Independent predictors of mortality were assessed using univariable and multivariable Cox proportional hazards regression analyses.

Results: The mean age of the cohort was 36.0±12.8 years, and 92.9% of patients were female. Over the 20-year accrual period, 20 patients (10.9%) died. The median follow-up duration was significantly shorter among deceased patients than among survivors [3.0 (1.0-7.0) vs. 32.0 (12.0-64.0) months; p<0.001], indicating predominantly early mortality. The leading cause of death was infection/sepsis (50.0%), with a substantial proportion related to thrombotic/antiphospholipid syndrome manifestations; however, antiphospholipid antibody profiles were not systematically available. In multivariable analysis, intensive care unit admission [hazard ratio (HR): 11.4, p<0.001], elevated baseline C-reactive protein (CRP) levels (HR: 1.02 per 1 mg/L increase, p=0.04), and lower serum albumin levels (HR: 0.31 per 1 g/dL increase, p=0.008) were independently associated with increased mortality risk. Pulse steroid therapy was associated with improved survival

Özet

Amaç: Sistemik lupus eritematozus (SLE) mortalitesi, hastalık aktivitesi, organ tutulumu ve tedaviye bağlı komplikasyonlar arasındaki karmaşık etkileşimi yansıtır. Bu çalışma, 20 yıllık hasta dahil edilme dönemi boyunca değişken bireysel takip süreleri olan bir üçüncü basamak SLE kohortunda, demografik, klinik ve laboratuvar parametrelerinin sağkalım üzerine etkilerini değerlendirmeyi ve mortalitenin bağımsız prediktörlerini belirlemeyi amaçladı.

Yöntem: 2005-2025 yılları arasında üçüncü basamak bir üniversite hastanesinde izlenen ve Amerikan Romatoloji Derneği/Avrupa Romatoloji Dernekleri Birliği sınıflama kriterlerini karşılayan 184 SLE hastası retrospektif olarak analiz edildi. Klinik bulgular, başlangıç laboratuvar parametreleri ve sağkalım sonuçları kaydedildi. Takip süreleri, simetrik olmayan dağılımları nedeniyle medyan (çeyrekler arası aralık) ile raporlandı. Mortalitenin bağımsız prediktörleri, tek değişkenli ve çok değişkenli Cox orantılı risk regresyon analizleri ile değerlendirildi.

Bulgular: Kohortun ortalama yaşı 36,0±12,8 yıl ve hastaların %92,9'u kadındı. Yirmi yıllık hasta dahil edilme döneminde 20 hasta (%10,9) hayatını kaybetti. Medyan takip süresi, ölen hastalarda sağ kalanlara göre anlamlı olarak daha kısaydı [3,0 (1,0-7,0) vs. 32,0 (12,0-64,0) ay, p<0,001] ve ağırlıklı olarak erken mortaliteyi gösteriyordu. Ölümün başlıca nedeni enfeksiyon/sepsis (%50,0) idi; trombotik/antifosfolipid sendromu ilişkili olaylar da önemli oranda yer almakta olup, antifosfolipid antikoru profilleri sistematik olarak mevcut değildi. Çok değişkenli analizde, yoğun bakım ünitesine kabul [tehlike oranı (HR): 11,4, p<0,001], yüksek başlangıç C-reaktif protein düzeyleri (HR: 1,02, 1 mg/L artış başına, p=0,04) ve düşük serum albümin düzeyleri (HR: 0,31, 1 g/dL artış başına, p=0,008) mortalite riskini bağımsız olarak artıran faktörler olarak saptandı. Pulse steroid tedavisi sağkalım

Correspondence / İletişim: Lec. MD, Zeynel Abidin Akar,
Dicle University Faculty of Medicine, Department of Physical Therapy and Rehabilitation, Division of Rheumatology, Diyarbakır, Türkiye
E-mail: zeynelabidin_akar@yahoo.com **ORCID ID:** orcid.org/0009-0003-2684-165X
Received / Geliş Tarihi: 13.01.2026 **Accepted / Kabul Tarihi:** 18.02.2026 **Publication Date / Yayın Tarihi:** 27.03.2026

Cite this article as / Atıf: Akar ZA, Yıldırım D. Twenty-year retrospective analysis of mortality risk factors in patients with systemic lupus erythematosus: a single-center cohort with variable individual follow-up. J Turk Soc Rheumatol. 2026;18(1):98-107

Abstract

(HR: 0.38, p=0.033). Causality cannot be inferred. Notably, the presence of lupus nephritis was associated with reduced mortality (HR: 0.09, p=0.035), which likely reflects more intensive monitoring and treatment in this subgroup.

Conclusion: Mortality in this cohort was primarily driven by acute inflammatory burden and the need for critical care, rather than by chronic organ damage. The "nephritis paradox" likely reflects an association with proactive management rather than a direct protective effect. These findings underscore the need for vigilant early risk stratification to mitigate acute, non-renal complications such as sepsis.

Keywords: Systemic lupus erythematosus, mortality, nephritis, C-reactive protein, albumin, APS, risk factors, survival analysis

Öz

ile ilişkili bulundu (HR: 0,38, p=0,033); nedensellik çıkarılamaz. İlginç bir şekilde, lupus nefriti varlığı mortalitenin azalmasıyla ilişkiliydi (HR: 0,09, p=0,035); bu durum muhtemelen bu alt grupta daha yoğun izlem ve tedavi uygulanmasıyla ilgilidir.

Sonuç: Bu kohortta mortalite, kronik organ hasarından ziyade akut enflamatuvar yük ve kritik bakım gereksinimi tarafından yönlendirilmektedir. "Nefrit paradoksu", doğrudan koruyucu bir etki yerine proaktif yönetimle ilişkili gibi görünmektedir. Bulgular, sepsis gibi akut, renal dışı komplikasyonları azaltmak için erken risk stratifikasyonunun önemini vurgulamaktadır.

Anahtar Kelimeler: Sistemik lupus eritematozus, mortalite, nefrit, C-reaktif protein, albümin, APS, risk faktörleri, sağkalım analizi

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with an incompletely understood etiology that predominantly affects young adults, particularly women of reproductive age.[1] It is characterized by widespread autoantibody production and immune complex deposition resulting from a loss of immune tolerance, leading to multi-organ involvement, including the skin, joints, kidneys, hematologic system, cardiopulmonary system, and nervous system.[2] The clinical course of SLE is highly heterogeneous, ranging from mild mucocutaneous manifestations to life-threatening multi-organ failure. This variable presentation, coupled with the relapsing nature of disease flares, necessitates a meticulous, multidisciplinary approach to diagnosis, treatment, and longitudinal follow-up.[3] Epidemiological studies in Türkiye indicate that while the overall clinical characteristics of Turkish SLE patients are broadly comparable to European cohorts, significant regional variations exist in organ involvement and mortality patterns.[4,5] Mortality in SLE may result not only from chronic organ damage but also from acute complications such as infections, sepsis, or thrombotic events, including those related to antiphospholipid syndrome (APS). Understanding these local disease patterns and the variable duration of patient follow-up in hospital-based cohorts is essential for improving patient survival and managing the high burden of disease activity often observed in tertiary care settings.

SLE is associated with high mortality due to its multisystem involvement and the risk of severe complications.[6] Key determinants of SLE-related mortality reported in the literature include disease activity indices, specific organ involvement, and concomitant complications.[7] In particular, renal involvement [lupus nephritis (LN)], cardiovascular events, pulmonary complications, recurrent flares, thrombotic events including those related to APS, and the need for intensive care unit (ICU) admission have been identified as the strongest predictors of poor prognosis.[8] Recent data from large Turkish cohorts indicate that infections, sepsis, and renal flares remain the leading causes of early mortality, consistent with global patterns.[9] Beyond clinical manifestations, laboratory parameters are crucial for mortality risk stratification. Systemic inflammation, reflected by elevated C-reactive protein (CRP) levels, and hypoalbuminemia—which serves as a surrogate marker for both nutritional status and severe organ dysfunction—are recognized as important biomarkers associated with increased mortality risk.[8] It is important to note that associations between treatment interventions (e.g., immunosuppressive therapy) and survival outcomes may reflect confounding factors such as closer monitoring of high-risk patients, rather than a direct protective effect. Notably, the effect of specific organ involvement on mortality remains a topic of ongoing debate. In some tertiary care centers, classical risk factors such as nephritis may show unexpected associations with survival, a phenomenon often attributed to "treatment-effect bias", whereby high-risk patients receive closer monitoring and more aggressive therapy compared with those with non-renal SLE manifestations.[10]

Despite significant advances in management, data on SLE-related mortality remain limited, particularly regarding outcomes from specialized tertiary centers in Türkiye with extended accrual periods, rather than data from individual long-term follow-up. While previous studies have identified general risk patterns, comprehensive evaluations of the interplay between baseline laboratory biomarkers, specific organ involvement, thrombotic events [including (APS)], and contemporary treatment strategies are scarce.[11] Much of the existing literature is constrained by smaller cohorts and variable follow-up durations, which hinder the systematic assessment of early- and late-stage complications, acute inflammatory events, and chronic organ damage.[12]

To address this gap, the present study evaluated a hospital-based SLE cohort accrued over a 20-year period (2005-2025), rather than through individual long-term follow-up. Our primary objective was to identify independent predictors of mortality by integrating demographic characteristics, baseline clinical manifestations—including thrombotic events and APS when documented—and laboratory biomarkers of systemic

inflammation. By analyzing outcomes over the study period, we aimed to refine risk stratification and provide insights into how contemporary management strategies influence survival patterns in a high-acuity SLE population, while acknowledging the limitations of incomplete antiphospholipid antibody (aPL) profiling and variable follow-up durations.

Materials and Methods

Study Design and Ethical Approval

This retrospective, single-center, observational cohort study was conducted at a tertiary referral center. Medical records of 184 patients diagnosed with SLE who fulfilled the 2019 the European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR) classification criteria and who were followed at the Department of Rheumatology, Dicle University Hospital between January 2005 and January 2025 were reviewed. This represents a 20-year cohort accrual period rather than an individual long-term follow-up. The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine (approval no: 4, date: 24.12.2025). Given the retrospective design and use of anonymized archival data, the requirement for written informed consent was waived. All procedures adhered to the ethical principles of the Declaration of Helsinki and complied with national regulations on patient data confidentiality.

Study Population and Selection Criteria

The study cohort included adult patients (aged ≥18 years) who fulfilled the 2019 EULAR/ACR and/or 1997 updated ACR classification criteria for SLE.[13,14] To ensure data integrity and clinical relevance, patients were required to have:

1. A confirmed SLE diagnosis based on the above criteria, including documentation of at least one clinical and one immunologic domain contributing to classification (for patients without major organ involvement).

2. Regular follow-up at the rheumatology department for a minimum of three months, unless death occurred earlier.

3. Complete baseline laboratory and clinical data at study inclusion.

Patients with overlapping autoimmune syndromes (e.g., mixed connective tissue disease) or incomplete medical records regarding primary outcomes (mortality and major SLE-related events) were excluded. The patient selection process and exclusion criteria are summarized in the study flow chart (Figure 1).

Some patients classified as "non-organ-involving SLE" met the criteria based on combinations of hematologic, mucocutaneous, and serologic domains and had no major organ involvement. The presence of aPL-related events was recorded descriptively when available; however, systematic aPL profiling was not consistently performed, precluding formal assessment of APS-related mortality.

Data Collection and Definitions

Patient data were systematically extracted from physical hospital archives and the electronic medical record system. To ensure consistency across the 20-year study period, a standardized data abstraction form was used. Baseline demographic and clinical characteristics included age at diagnosis, sex, and follow-up duration (calculated from diagnosis to last visit or death).

Disease flares were originally defined by SLE disease activity index 2000 (SLEDAI-2K) as an increase of >4 points. However, because SLEDAI-2K data were missing in a substantial proportion of visits, flares were operationally defined based on clinical deterioration requiring therapy escalation, as determined from chart review. This approach was applied consistently across the cohort, and flare-related findings should be interpreted cautiously.

Clinical severity was further evaluated by total hospitalizations and ICU admissions. Organ involvement was adjudicated according to ACR classification guidelines and corroborated by biopsy, imaging, and clinical reports. Specific definitions included:

• LN: biopsy-confirmed ISN/RPS class or persistent proteinuria >0.5 g/day or presence of cellular casts.

• Neuropsychiatric SLE: seizures, psychosis, or organic brain syndrome after exclusion of metabolic or infectious causes.

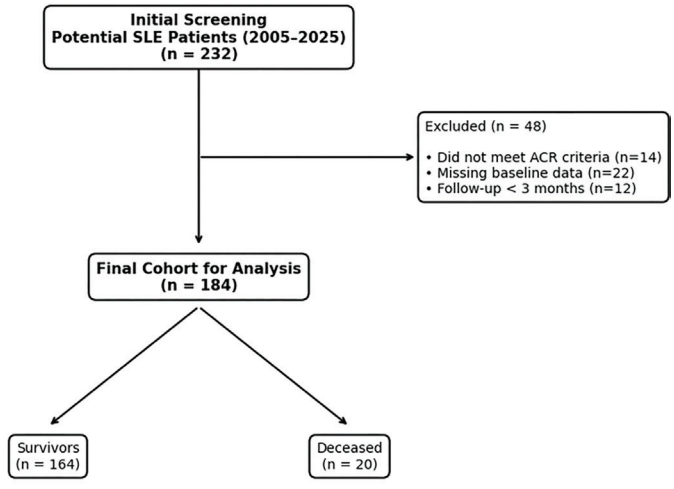

Figure 1. Flowchart of patient selection and study design. The flowchart illustrates the inclusion and exclusion process of the study cohort. Between 2005 and 2025, a total of 232 patients with suspected SLE were screened. Of these, 48 patients were excluded based on predefined criteria, including failure to meet the ACR/EULAR classification criteria, missing baseline data, or short-term follow-up unrelated to mortality outcomes. The final analysis included 184 patients, who were stratified into survivors (n=164) and deceased (n=20) groups for the evaluation of mortality risk factors

ACR: American College of Rheumatology, EULAR: The European Alliance of Associations for Rheumatolog, SLE: Systemic lupus erythematosus

• Serositis: clinically or radiologically confirmed pleuritis or pericarditis (ultrasonography/computed tomography).

Laboratory parameters included inflammatory markers (CRP and erythrocyte sedimentation rate) and complement levels. Hypocomplementemia was defined as C3 <80 mg/dL and C4 <15 mg/dL; complement levels were analyzed as categorical variables (normal vs. low). Serologic assessments included antinuclear antibody (immunofluorescence), anti-dsDNA (ELISA), and anti-Smith antibodies, recorded as present or absent.

Immunosuppressive treatment history included major modalities such as pulse steroid therapy (intravenous methylprednisolone ≥250 mg/day for 3 consecutive days) and cyclophosphamide (cumulative or induction), to evaluate associations with survival. Observed associations should be interpreted as associative rather than causal, and potential confounding by indication or immortal time bias should be acknowledged. Importantly, immunosuppressive therapies are well-known to increase the risk of infection and sepsis; therefore, any observed survival association should not be interpreted as a biological protective effect.

Statistical Analysis

All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests, complemented by visual inspection of histograms and Q-Q plots.

Descriptive statistics are presented as mean ± standard deviation for normally distributed variables. Due to the skewed distributions of follow-up periods and inflammatory markers, non-normally distributed data are reported as medians [interquartile range (IQR)]. Categorical variables are expressed as counts (n) and percentages (%).

Comparisons between survivors and deceased patients were performed using independent-samples t-tests or Mann-Whitney U tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables, as appropriate. Cumulative survival probabilities were estimated using the Kaplan-Meier method, and subgroup differences were assessed with the log-rank test.

To identify independent predictors of mortality, Cox proportional hazards regression models were constructed. Variables with $p<0.10$ in univariable analyses, along with clinically relevant parameters such as organ involvement, complement levels, hypoalbuminemia, and treatment modalities, were included in the multivariable model using backward stepwise selection.

• Albumin hazard ratio (HR) directionality: albumin was modeled per 1 g/dL increase; an HR <1 indicates a protective effect of higher albumin, consistent with descriptive findings.

• Complement variables: both low C3 and low C4 were evaluated using univariable Cox models. They were excluded from the final multivariable model due to collinearity with CRP and clinical severity markers.

• Treatment effects (pulse steroids, immunosuppressives): observed associations with mortality should be interpreted as associational rather than causal, acknowledging the potential for confounding by indication, immortal time bias, or enhanced clinical monitoring in high-risk patients.

• APS/aPL limitation: due to incomplete aPL profiling, the impact of antiphospholipid syndrome-related events on mortality is described qualitatively, and no causal inference is made.

Results are presented as HRs with 95% confidence intervals (CIs); two-sided p-values <0.05 are considered statistically significant.

Results

A total of 184 patients diagnosed with SLE were included in this longitudinal, hospital-based cohort. The population demonstrated a marked female predominance (n=171, 92.9%), with a mean age at diagnosis of 36.0±12.8 years. The median follow-up duration for the cohort was 14.0 months (IQR: 5.0-42.0), reflecting a skewed distribution due to predominantly early mortality among a subset of patients. Although the mean follow-up was 29.1±38.7 months, the wide variance underscores the heterogeneous nature of patient trajectories across the 20-year study period.

Regarding organ involvement, LN was the most frequent manifestation, observed in 58 patients (31.5%). APS or aPL positivity, documented in 35 patients (19.0%), contributed substantially to thrombotic events and mortality in this cohort. Hematologic involvement was present in 27 patients (14.7%) and neuropsychiatric SLE was present in 8 patients (4.3%). Baseline immunological evaluation revealed positivity for anti-double-stranded DNA (anti-dsDNA) in 83.2% (n=153). Hypocomplementemia was common: low C3 and C4 levels were detected in 52.1% and 44.0% of patients, respectively (Table 1).

During the 20-year study period, 20 patients (10.9%) died. There were no significant differences between survivors and deceased patients with respect to age ($p=0.781$) or sex ($p=0.665$). However, the median follow-up duration was markedly shorter for deceased patients [3.0 months (IQR: 1.0-7.0)] than survivors [32.0 months (IQR: 12.0-64.0); $p<0.001$], reflecting predominantly early mortality after diagnosis.

Markers of clinical severity were significantly more pronounced in the deceased group. These patients experienced a higher mean number of hospitalizations (2.5±2.2 vs. 0.8±1.4, $p<0.001$) and a greater frequency of disease flares (1.9±1.8 vs. 1.1±1.4, $p=0.024$). Due to incomplete SLEDAI-2K data, flares

were primarily defined based on clinical deterioration requiring treatment escalation, as documented in medical charts. ICU admission was markedly more frequent among deceased patients (80.0% vs. 19.5%, p<0.001).

Baseline laboratory analyses demonstrated that deceased patients had higher median CRP levels (21.5 mg/L vs. 3.5 mg/L, p<0.001) and lower median serum albumin levels (3.3 g/dL vs. 3.8 g/dL, p<0.001). While anti-dsDNA positivity was similar between groups, deceased patients had a higher prevalence of low C4 levels (65.0% vs. 41.4%, p=0.041) and a non-significant trend toward lower C3 levels (70.0% vs. 50.0%, p=0.084).

Notably, LN was less frequent among deceased patients (5.0% vs. 34.8%, p=0.012), consistent with the so-called "nephritis paradox", which likely reflects closer monitoring and more intensive treatment in nephritis patients. Conversely, APS or aPL positivity was more common among deceased patients, highlighting the contribution of thrombotic complications to mortality (Table 1).

Significant differences in treatment strategies were observed between survivors and non-survivors. Antimalarial therapy with hydroxychloroquine was administered to nearly all survivors (96.3%) but to fewer deceased patients (65.0%, p<0.001). Pulse methylprednisolone therapy was administered more frequently to survivors than to deceased patients (39.6% vs. 15.0%, p=0.033). However, this observation reflects an association and should not be interpreted as causal, since higher-risk patients may have received different treatment intensities or closer monitoring.

The distribution of daily prednisolone doses differed significantly between groups (p<0.001). Approximately half of the survivors were maintained on moderate-dose prednisolone (7.5-30 mg/day), whereas the majority of deceased patients (60.0%) received high-dose glucocorticoids (>30 mg/day). Among the immunosuppressive agents, use of mycophenolate mofetil was more common in survivors (30.5% vs. 10.0%, p=0.048), whereas use of cyclophosphamide and azathioprine did not differ significantly between groups (Table 2).

An in-depth analysis of the 20 patients who died during follow-up revealed that mortality was predominantly driven by acute complications. The leading causes of death were infection and sepsis, accounting for 50.0% (n=10) of all fatalities. This was followed by SLE-related acute organ failure (including refractory alveolar hemorrhage and multi-organ dysfunction) in 25.0% (n=5) of cases. Cardiovascular events, such as myocardial infarction or stroke, were responsible for 15.0% (n=3) of deaths, while the remaining 10.0% (n=2) were attributed to other or unspecified complications. Kaplan-Meier survival analysis demonstrated that the risk of mortality was highest during the early months following diagnosis, with survival curves stabilizing thereafter (Figure 2).

Table 1. Baseline clinical, laboratory, and immunological characteristics of the study cohort according to survival status

Variable	Total cohort (n=184)	Survivors (n=164)	Deceased (n=20)	p-value
Demographics				
Age, years	36.0±12.8	35.9±12.8	36.9±13.0	0.781
Female, n (%)	171 (92.9)	152 (92.7)	19 (95.0)	0.665
Disease follow-up & activity				
Follow-up duration, months, median (IQR)	14.0 (5.0-42.0)	32.0 (12.0-64.0)	3.0 (1.0-7.0)	<0.001
Total hospitalizations	1.0±1.6	0.8±1.4	2.5±2.2	<0.001
Number of disease flares*	1.2±1.5	1.1±1.4	1.9±1.8	0.024
Clinical involvement, n (%)				
Lupus nephritis	58 (31.5)	57 (34.8)	1 (5.0)	0.012
Antiphospholipid syndrome	35 (19.0)	31 (18.9)	4 (20.0)	0.892
Hematologic involvement	27 (14.7)	27 (16.5)	0 (0.0)	0.114
Laboratory findings (baseline), median (IQR)				
C-reactive protein (mg/L)	4.5 (1.6-13.9)	3.5 (1.4-10.3)	21.5 (7.7-35.8)	<0.001
Serum albumin (g/dL)	3.7 (3.3-4.1)	3.8 (3.4-4.1)	3.3 (2.9-3.7)	<0.001
Immunological findings, n (%)				
Low C3	96 (52.1)	82 (50.0)	14 (70.0)	0.084
Low C4	81 (44.0)	68 (41.4)	13 (65.0)	0.041
Anti-dsDNA positivity	153 (83.2)	138 (84.1)	15 (75.0)	0.322

Data are presented as mean ± SD, median (IQR), or number (n) and percentage (%). Follow-up duration represents time from diagnosis to last visit or death and is reported as median (IQR) due to skewed distribution. Disease flare was defined as an increase of >4 points in the SLEDAI-2K score or clinical worsening requiring therapeutic escalation. Baseline laboratory and immunological parameters were obtained at study inclusion, prior to treatment escalation. Hypocomplementemia was defined according to local laboratory reference ranges (C3 <80 mg/dL, C4 <15 mg/dL). ANA: Antinuclear antibody, anti-dsDNA: Anti-double-stranded DNA antibody, Anti-Sm: Anti-Smith antibody, APS: Antiphospholipid syndrome, C3: Complement component 3, C4: Complement component 4, CRP: C-reactive protein, ICU: Intensive care unit, IQR: Interquartile range, SLE: Systemic lupus erythematosus, SD: Standard deviation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000

In multivariable Cox proportional hazards analysis, ICU admission emerged as the strongest independent predictor of mortality (HR: 11.4; 95% CI: 4.2-31.5; p<0.001). Among laboratory parameters, each 1 mg/L increase in CRP was associated with a 2% increase in mortality risk (HR: 1.02; p=0.04). Serum albumin was modeled per 1 g/dL increase; higher levels were associated with reduced mortality risk (HR: 0.31; p=0.008), which is consistent with lower albumin being linked to worse outcomes.

Pulse steroid therapy was observed more frequently among survivors (HR: 0.38; p=0.033), which reflects an association rather than causation and may partly indicate intensified monitoring or treatment in higher-risk patients. Similarly, the presence of LN was associated with improved observed survival (HR: 0.09; p=0.035), likely reflecting closer clinical surveillance and proactive management of patients with renal involvement (Table 3).

Table 2. Comparison of treatment characteristics between survivors and deceased patients with SLE

Treatment modality, n (%)	All cohort (n=184)	Survivors (n=164)	Deceased (n=20)	p-value
Glucocorticoids (ever)	175 (95.1)	156 (95.1)	19 (95.0)	0.999
Pulse methylprednisolone	68 (37.0)	65 (39.6)	3 (15.0)	0.033
Daily prednisolone dose				<0.001
Low dose (<7.5 mg/day)	42 (22.8)	40 (24.4)	2 (10.0)	
Moderate dose (7.5-30 mg/day)	88 (47.8)	82 (50.0)	6 (30.0)	
High dose (>30 mg/day)	54 (29.4)	42 (25.6)	12 (60.0)	
Antimalarials (hydroxychloroquine)	171 (92.9)	158 (96.3)	13 (65.0)	<0.001
Immunosuppressants (any)	124 (67.4)	115 (70.1)	9 (45.0)	0.024
Cyclophosphamide	42 (22.8)	38 (23.2)	4 (20.0)	0.751
Azathioprine	78 (42.4)	72 (43.9)	6 (30.0)	0.235
Mycophenolate mofetil	52 (28.3)	50 (30.5)	2 (10.0)	0.048
Rituximab	12 (6.5)	11 (6.7)	1 (5.0)	0.999

Data are presented as number (n) and percentage (%). Pulse methylprednisolone was defined as intravenous methylprednisolone ≥250 mg/day administered for three or more consecutive days. Daily prednisolone dose categories (<7.5 mg/day, 7.5-30 mg/day, >30 mg/day) were compared using a chi-square test for trend. Other immunosuppressive agents include cyclophosphamide, azathioprine, mycophenolate mofetil, and rituximab. HCQ: Hydroxychloroquine, SLE: Systemic lupus erythematosus

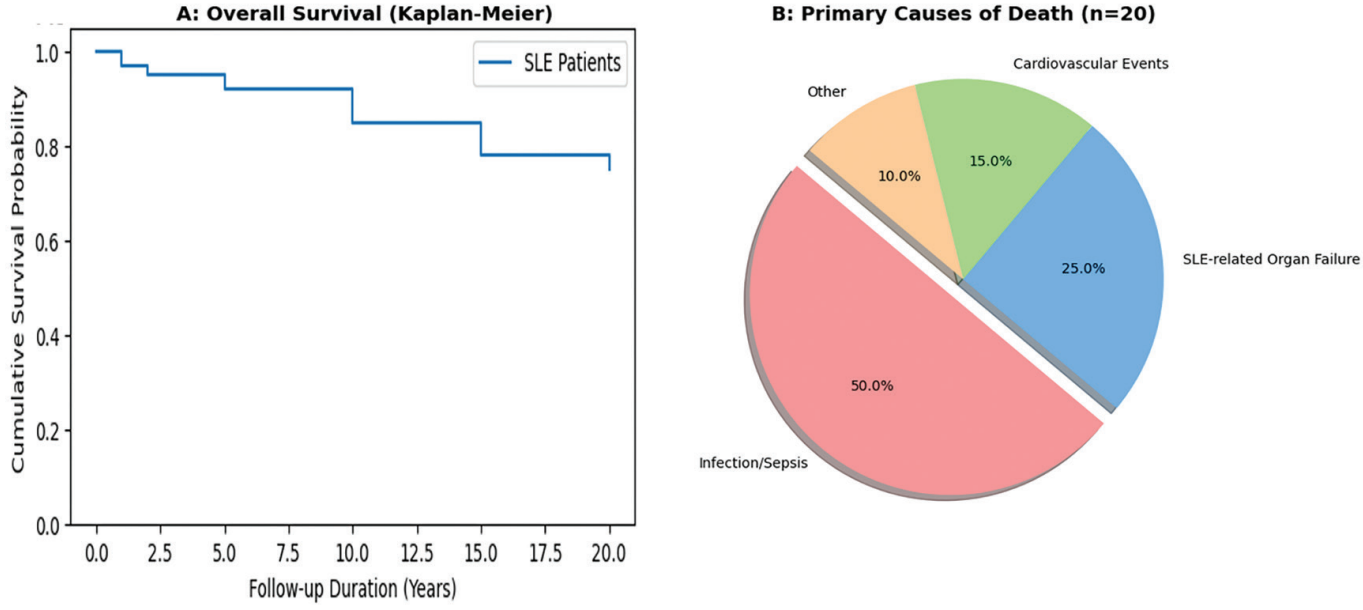

Figure 2. Survival characteristics of the study cohort. (A) Kaplan-Meier survival curve showing the probability of survival over time using longitudinal follow-up data (n=184). The X-axis represents the duration of follow-up (years), while the Y-axis indicates the cumulative survival probability. (B) Distribution of the primary causes of death among the deceased patients (n=20), with infection and sepsis accounting for 50% of the total mortality
SLE: Systemic lupus erythematosus

Table 3. Univariate and multivariate cox proportional hazards analysis of mortality risk factors in SLE patients				
Feature	**Univariate analysis HR (95% CI)**	**p-value**	**Multivariate analysis HR (95% CI)**	**p-value**
Clinical severity				
ICU admission (yes)	15.5 (6.2-38.9)	<0.001	11.4 (4.2-31.5)	<0.001
Organ involvement				
Presence of nephritis	0.13 (0.02-0.99)	0.048	0.09 (0.01-0.78)	0.035
Laboratory parameters				
CRP (per 1 mg/L increase)	1.03 (1.02-1.05)	<0.001	1.02 (1.00-1.04)	0.04
Albumin (per 1 g/dL increase)	0.20 (0.07-0.58)	0.003	0.31 (0.11-0.88)	0.008
Treatment factors				
Pulse steroid therapy	0.42 (0.21-0.85)	0.015	0.38 (0.15-0.92)	0.033
Cyclophosphamide use	1.03 (0.33-3.20)	0.96	—	—
Multivariate model was constructed using Cox proportional hazards regression, including variables with p<0.10 in univariate analysis and adjusted for age and sex. CI: Confidence interval, CRP: C-reactive protein, HR: Hazard ratio, ICU: Intensive care unit. "—" indicates that the variable was not included in the multivariate analysis				

Discussion

This study, which represents two decades of clinical experience (2005-2025) at a tertiary referral center, identifies key clinical and laboratory determinants of mortality in a cohort of 184 patients with SLE. The overall mortality rate was 10.9% (n=20), with a notable concentration of deaths occurring early in the disease course. Mortality in this cohort was predominantly driven by acute complications, particularly infection and sepsis, rather than late-stage chronic organ damage.

In multivariable analyses, ICU admission (HR: 11.4), elevated baseline CRP levels, and hypoalbuminemia were the strongest independent predictors of mortality. Pulse steroid therapy and the presence of LN were associated with better observed survival (HR: 0.38 and 0.09, respectively), likely reflecting closer monitoring and more aggressive management in these higher-risk subgroups, rather than a direct protective effect. These associations should be interpreted cautiously because confounding by indication and immortal time bias may contribute to the observed outcomes.

Collectively, these results delineate a high-risk "inflammatory phenotype" predisposed to acute complications, emphasizing the importance of early risk stratification, vigilant clinical monitoring, and prompt intervention to improve survival. Limitations due to incomplete aPL profiling should be acknowledged, as APS-related events contributed substantially to mortality in a subset of patients and systematic assessment was not uniformly available.

The mortality risk factors identified in our study largely align with prognostic profiles reported in both global and Turkish cohorts. The observed overall mortality rate of 10.9% is comparable to previous Turkish studies: Pamuk et al.[4] reported a mortality rate of approximately 9.1%, and Artim-Esen et al.[5] similarly described early mortality as predominantly associated with high disease activity. In our cohort, elevated CRP and low serum albumin levels were associated not only with the acute-phase response but also with profound systemic inflammation and poor prognosis. These findings are consistent with previous observations that high baseline disease activity and inflammatory markers are linked to early mortality in Turkish patients with SLE. Notably, our results reinforce the concept that in severe SLE, often complicated by secondary infections, these biomarkers—reflecting a high-risk "acute inflammatory phenotype"—are associated with short-term mortality. Limitations related to incomplete aPL profiling should be acknowledged because APS-related events likely contributed to mortality in some patients, and a systematic assessment of these events was not available.

This finding is supported by our data, which show that 50.0% of deaths were due to infection or sepsis. The short median follow-up of 3.0 months among the deceased group (Table 1) further highlights the potential role of a high systemic inflammatory burden—objectively reflected by elevated CRP and hypoalbuminemia—in predisposing patients to rapid clinical deterioration and the need for intensive care.[8,11] As shown by our cumulative mortality analysis (Figure 2A), the risk of death is highest shortly after diagnosis. Accordingly, CRP and albumin levels are associated with this high-risk "acute inflammatory phenotype" and may help identify patients at increased risk of sepsis-related mortality. Importantly, associations observed between pulse steroid therapy or other immunosuppressive interventions and survival should be interpreted cautiously, as these findings reflect correlations rather than causal effects and may be influenced by confounding factors such as treatment intensity, closer monitoring, or survivor bias. Early recognition of this high-risk profile may facilitate closer clinical surveillance and informed decision-making regarding supportive care and therapeutic intensity.

On the other hand, the impact of LN on mortality remains a topic of ongoing debate.[15] Although LN has traditionally been considered a marker of severe organ involvement and a potential risk factor for death, our observation of an inverse

association (HR: 0.09; Table 3) aligns with several contemporary cohorts reporting heterogeneous survival outcomes.[16] This apparent paradox likely reflects a combination of factors, including intensified monitoring, closer clinical follow-up, and more aggressive immunosuppressive therapy in patients with renal involvement, rather than a direct protective effect of LN itself. Consequently, these findings should be interpreted as associations, and causal inferences cannot be drawn from this observational study.

At our tertiary center, patients with renal involvement are generally monitored more closely and often receive more intensive therapy. Treatment data (Table 2) show that survivors—many of whom had LN—were significantly more likely to receive antimalarials (hydroxychloroquine, 96.3% vs. 65.0%, $p<0.001$) and mycophenolate mofetil (mycophenolate mofetil, 30.5% vs. 10.0%, $p=0.048$) than deceased patients. Additionally, the higher frequency of pulse methylprednisolone use among survivors (39.6% vs. 15.0%, $p=0.033$) suggests that patients with major organ involvement, such as LN, were managed with more intensive anti-inflammatory regimens. These observations likely reflect an association between proactive therapeutic strategies and improved short-term survival, rather than a direct protective effect of renal involvement itself. Such intensive management may mitigate the risk of acute, potentially fatal complications—including sepsis and severe disease flares—that were the predominant causes of death in our cohort (Figure 2B).[17]

Consistent with our findings, multivariable analysis identified pulse steroid therapy as an independent factor associated with improved short-term survival (HR: 0.38). This treatment modality was more commonly used in survivors, particularly among patients with LN. Importantly, most deaths in our cohort occurred early after diagnosis and were primarily related to acute sepsis rather than chronic organ damage.[18] These observations suggest that intensive monitoring and early immunosuppressive therapy are associated with lower early mortality, rather than a direct protective effect of LN. Conversely, patients without major organ-specific involvement—sometimes classified as "non–organ-involving SLE"—may still experience severe systemic inflammation, which can lead to rapid clinical deterioration if not addressed with comparable vigilance.[8,19,20] Furthermore, a substantial proportion of early deaths were related to thrombotic complications potentially associated with APS or aPL positivity. Because aPL profiling in our cohort was incomplete, this relationship should be interpreted with caution, and we emphasize that APS-related events may significantly contribute to early mortality in patients without classic organ involvement. Overall, these findings highlight that in SLE, early mortality risk is influenced less by the specific organ affected and more by the timely recognition and management of acute systemic inflammation and thrombotic complications.

The strong association between ICU admission and mortality (HR: 11.4; Table 3) indicates that patients requiring critical care often present with a high-risk "inflammatory phenotype", characterized by elevated CRP and hypoalbuminemia. These laboratory abnormalities serve as markers of systemic inflammation and metabolic depletion, identifying a critical window of vulnerability during which patients are at increased risk for refractory sepsis and multi-organ failure. A subset of patients who died had thrombotic events compatible with APS. However, a formal APS classification could not be established in many cases due to incomplete aPL profiling during the long accrual period. Consequently, while APS-compatible manifestations were observed among non-survivors, a statistically robust association between APS and mortality could not be demonstrated. These findings should therefore be interpreted descriptively, and no causal inference regarding APS-related mortality can be made.

Importantly, classification as non–organ-involving SLE does not preclude the occurrence of severe systemic complications. In our cohort, several patients without classical major organ involvement (such as LN or neuropsychiatric SLE) nonetheless fulfilled classification criteria in the hematologic, mucocutaneous, and serologic domains and later developed thrombotic or hemorrhagic complications. This highlights the heterogeneity of SLE phenotypes and underscores that the absence of traditional organ involvement does not necessarily imply a benign disease course.

Conversely, the observed survival advantage in patients with LN (HR: 0.09) highlights that early mortality is not inevitable. The "clinical vigilance" inherent in the management of renal involvement—as reflected by the more frequent use of pulse steroids (HR: 0.38) and intensive immunosuppressive regimens (Table 2)—was associated with improved survival, likely because of closer monitoring and timely intervention during acute flares. However, these therapies carry inherent risks, including an increased susceptibility to infection, underscoring the need to balance immunosuppressive intensity with vigilant infection prophylaxis. Our findings indicate that in contemporary SLE cohorts, survival is determined not only by the organ involved but also by the effectiveness of clinical strategies that mitigate both inflammatory and thrombotic complications. Early recognition and management of high-risk profiles, including the potential contribution of APS-related events, are essential for reducing preventable early deaths through the combined control of disease activity and maintenance of physiological reserve.

Similarly, ICU admission and the absence of LN among non-survivors likely reflect extreme acute disease severity rather than protective or harmful effects of specific organ involvement. Together, these findings suggest that early mortality in SLE is driven predominantly by acute systemic inflammatory burden and critical illness, rather than by cumulative organ damage alone.

A primary strength of this study is its 20-year accrual period, enabling the identification of early mortality patterns and risk profiles. Integration of comprehensive laboratory panels with detailed clinical data, including ICU admissions and treatment modalities, provides a practical framework for risk stratification in high-acuity SLE patients. Multivariable Cox regression models were used to evaluate associations between inflammatory biomarkers and clinical indicators; residual confounding, including potential APS contributions, was acknowledged. The single-center design enhances internal validity by reducing inter-center variability.

Study Limitations

Despite the valuable insights provided by our study, several limitations should be acknowledged. First, the retrospective design may have posed challenges in consistently capturing longitudinal clinical parameters and standardized disease activity scores (e.g., SLEDAI-2K), which were frequently missing. As a result, disease flares were sometimes inferred from chart review and from escalation of therapy rather than by objective scoring, which may have reduced the precision of flare-related analyses. Second, the single-center design of this study, conducted at a tertiary referral hospital, may limit the generalizability of our findings to SLE populations in primary-care settings or other geographic regions. Third, although our cohort size (n=184) was sufficient to identify major independent risk factors, the relatively small number of deaths (n=20) may have limited the statistical power to detect associations with less common manifestations, such as specific neuropsychiatric or cardiac involvement, in multivariable analyses. Fourth, systematic assessment of aPL profiles was not available for all patients; therefore, APS-related mortality and thrombotic risk could not be fully evaluated. This limitation should be considered when interpreting the contribution of APS to deaths in this cohort. In addition, because data were derived from hospital records, complications or minor flares occurring outside our center may not have been fully captured. Finally, the 20-year accrual period (2005-2025) encompassed substantial advances in SLE management, including evolving immunosuppressive protocols and the introduction of biologic therapies. Although major interventions, such as pulse steroids, were incorporated into our models, these temporal changes, together with potential confounding by indication, may have influenced the observed associations between treatment and outcomes, particularly regarding sepsis and infection-related mortality.

Conclusion

This study underscores the prognostic value of early risk stratification in patients with SLE, drawing on a 20-year accrual period at a tertiary referral center. Elevated CRP, hypoalbuminemia, frequent hospitalizations, and ICU admission were identified as practical, low-cost, and reliable predictors of increased mortality risk, with ICU admission showing the strongest association with poor outcomes. Importantly, our findings highlight a high-risk "inflammatory phenotype", which—if recognized early—may allow clinicians to intensify monitoring and implement proactive interventions to prevent acute, life-threatening complications, particularly sepsis. Additionally, the observed survival advantage in patients with LN reflects the potential benefits of intensive monitoring and aggressive management, rather than a direct protective effect. Limitations include incomplete aPL profiling, which may have influenced assessment of APS-related mortality. Overall, our 20-year experience demonstrates that vigilant attention to inflammatory and metabolic markers, coupled with tailored therapeutic strategies, is critical for improving early and long-term survival outcomes in SLE.

Ethics

Ethics Committee Approval: Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine (approval no: 4, date: 24.12.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A.A., D.Y., Concept: Z.A.A., D.Y., Design: Z.A.A., D.Y., Data Collection and Processing: Z.A.A., D.Y., Analysis or Interpretation: Z.A.A., D.Y., Literature Search: Z.A.A., D.Y., Writing: Z.A.A., D.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

References

1. Su X, Yu H, Lei Q, et al. Systemic lupus erythematosus: pathogenesis and targeted therapy. Mol Biomed. 2024;5:54.
2. Tsokos GC. The immunology of systemic lupus erythematosus. Nat Immunol. 2024;25:1332-43.
3. Ameer MA, Chaudhry H, Mushtaq J, et al. An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus. 2022;14:e30330.
4. Pamuk ON, Akbay FG, Dönmez 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.
5. Artim-Esen B, Şahin S, Çene E, et al. Comparison of disease characteristics, organ damage, and survival in patients with juvenile-onset and adult-onset systemic lupus erythematosus in a combined cohort from 2 tertiary centers in Turkey. J Rheumatol. 2017;44:619-25.
6. Lee YH, Song GG. Mortality in patients with systemic lupus erythematosus: a meta-analysis of overall and cause-specific effects. Lupus. 2024;33:929-37.

7. Lai CC, Sun YS, Chen WS, et al. Risk factors for mortality in systemic lupus erythematosus patients: Analysis of adult and pediatric cohorts in Taiwan. J Chin Med Assoc. 2022;85:1044-50.

8. He S, Tang C, Yu J, et al. Combining C reactive protein and serum albumin to predict 90-day mortality in systemic lupus erythematosus with serious community-acquired infections. Lupus Sci Med. 2021;8:e000505.

9. Kanık HK, Erden A, Yıldırım D, et al. Evolution of clinical characteristics and treatment strategies in Turkish SLE patients over two decades: a retrospective cohort study. Bratisl Med J. 2025;126:2329-36.

10. Artim-Esen B, Çene E, Şahinkaya Y, et al. Cluster analysis of autoantibodies in 852 patients with systemic lupus erythematosus from a single center. J Rheumatol. 2014;41:1304-10.

11. Üsküdar Cansu D, Üsküdar Teke H, Korkmaz C. Survival analysis of Turkish patients with systemic lupus erythematosus: older age at diagnosis affects mortality. Arch Rheumatol. 2017;32:141-8.

12. Murimi-Worstell IB, Lin DH, Nab H, et al. Association between organ damage and mortality in systemic lupus erythematosus: a systematic review and meta-analysis. BMJ Open. 2020;10:e031850.

13. Eilertsen GØ, Becker-Merok A, Nossent JC. The influence of the 1997 updated classification criteria for systemic lupus erythematosus: epidemiology, disease presentation, and patient management. J Rheumatol. 2009;36:552-9.

14. 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.

15. Reppe Moe SE, Molberg Ø, Strøm EH, Lerang K. Assessing the relative impact of lupus nephritis on mortality in a population-based systemic lupus erythematosus cohort. Lupus. 2019;28:818-25.

16. Luo W, Farinha F, Isenberg DA, Rahman A. Survival analysis of mortality and development of lupus nephritis in patients with systemic lupus erythematosus up to 40 years of follow-up. Rheumatology (Oxford). 2022;62:200-8.

17. Reppe Moe S, Haukeland H, Molberg Ø, Lerang K. Long-term outcome in systemic lupus erythematosus; knowledge from population-based cohorts. J Clin Med. 2021;10:4306.

18. Howe HS, Boey ML, Feng PH. Methylprednisolone in systemic lupus erythematosus. Singapore Med J. 1990;31:18-21.

19. Ponticelli C, Zucchelli P, Moroni G, Cagnoli L, Banfi G, Pasquali S. Long-term prognosis of diffuse lupus nephritis. Clin Nephrol. 1987;28:263-71.

20. Figueroa-Parra G, Cuéllar-Gutiérrez MC, González-Treviño M, et al. Impact of glucocorticoid dose on complete response, serious infections, and mortality during the initial therapy of lupus nephritis: a systematic review and meta-analysis of the control arms of randomized controlled trials. Arthritis Rheumatol. 2024;76:1408-18.