Damage Accumulation in Systemic Lupus Erythematosus and Its Relation to Disease Activity and Mortality

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ABSTRACT. ***Objective.*** To describe damage accrual and the interconnections between disease activity measures, damage accrual, and death in a Nordic lupus cohort.

Methods. Longitudinal study in the population-based Tromsø lupus cohort. Disease activity [SLE Disease Activity Index (SLEDAI)] and disease damage [by Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI)] were recorded for each visit. Weighted average SLEDAI scores (WAS) were calculated to correct for variable observation times. Development of damage (SDI > 0), severe damage (SDI ≥ 3), and death were used as separate endpoints. Univariate nonparametric analysis identified and hazard ratios (HR) by Cox regression techniques confirmed the independence of predictors for each outcome.

Results. Through 11.9 years of followup, 72 patients (46%) remained free of damage, 51 (32%) developed moderate damage, and 35 (22%) developed severe damage. SDI scores were higher in 37 nonsurvivors (23.4%; SDI 2.1) than in survivors (SDI 0.9; $p < 0.05$). Damage accrual was linear throughout the first decade of disease. The only independent predictor for SDI ≥ 3 was a WAS score > 3 (hazard ratio 2.34; 95% CI 1.1–4.9). Age > 40 years at diagnosis (HR 5.6, 95% CI 2.4–12.7) and WAS > 3 (HR 2.4, 95% CI 1.2–4.9) were significant predictors for death.

Conclusion. Damage accrual in SLE occurred in 54% of patients in a linear fashion over the first decade of disease. Global disease activity was the main determinant of damage accrual. Accrued damage was not an independent risk factor for death, which was predicted by age > 40 years and WAS > 3. (First Release July 15 2006; J Rheumatol 2006;33:1570–7)

Key Indexing Terms:
DAMAGE DISEASE ACTIVITY MORTALITY SYSTEMIC LUPUS ERYTHEMATOSUS

Over the last decades systemic lupus erythematosus (SLE) has evolved from a rapidly fatal disease into a chronic condition as impressive gains in shorter-term survival have been achieved through the more efficient use of immunomodulating drugs and the expanding arsenal of supportive therapy[1,2]. Longterm survival in patients with SLE, however, lingers far below control groups[3,4]. While late mortality is often related to the accelerated appearance of cardiovascular complications later in the disease course[5-9], various other types of organ damage such as pulmonary and renal insufficiency have a negative effect on longer-term survival[10,11]. The Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) is the preferred tool for measuring irreversible damage in SLE patients and reflects damage as the result of disease activity, drug toxicity, and comorbidity or any combination of these factors[12,13]. SDI has been shown to be valid and reproducible and has now been included in the recommended measures of outcome in SLE[14-16]. Originally meant to be a substitute for death as an outcome marker in the earlier phases of the disease, some studies reported that increasing SDI scores also predispose for mortality in SLE[17-19]. In addition, higher SDI scores significantly reduce the quality of life in lupus patients[20,21]. The current challenge for clinicians is to balance therapeutic measures to reduce early disease activity and mortality against the need to delay and preferably prevent longterm damage because of such treatment[22]. This delicate balancing act requires detailed knowledge of the process by which damage develops, especially in areas with opportunities to intervene. Damage accrual over time in SLE has been associated with fixed characteristics such as age, sex, and race[23–27], but amendable factors such as initial disease activity[28,29], disease activity over time[26], longer disease duration[25,30,31], and shorter time to occurrence of first damage[27,32] predict damage accrual as well. This study describes overall and organ-specific damage accrual using longterm followup data of a population-based, homogenous lupus cohort with free access to healthcare. Subsequent detailed analyses were performed to elucidate the complex relation between damage, disease activity, and mortality.

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MATERIALS AND METHODS

Patients. The Tromsø lupus cohort was a longitudinal population-based study of all SLE patients in the 2 northern-most counties in Norway. The cohort included only patients fulfilling at least 4 ACR criteria (1982 revision and 1997 update) for the classification of SLE[33,34], and detailed characteristics have been described[35]. SLE patients were followed by attending physicians of the sole rheumatology service in the area, who as a rule saw patients with quiescent disease twice annually, while control frequency was increased with concerns and signs of complications.

Data collection. Every hospital visit was registered in a database with the use of a predefined data sheet that recorded demographics, clinical findings, and medication, together with results of routine hematology and biochemistry analysis (including urine dipstick and microscopy findings), and discretional testing for antinuclear antibodies (ANA; by ELISA screen), with subsequent anti-dsDNA antibody and complement measurement. For each patient visit, disease activity was then calculated by an experienced rheumatologist with the use of the SLE Disease Activity Index (SLEDAI) score[36], while damage development was scored by SDI[12]. Information obtained directly from patients and indirectly from hospital records (including notes from other departments) and general practitioners was verified before inclusion in the relevant scoring systems. At the time of this analysis total followup consisted of 22.567 patient-months.

Definitions. Disease duration was the time interval from SLE research diagnosis (defined as fulfilling 4 ACR criteria) until last followup visit or time of death. In analyzing the distribution of SDI scores over time, the DI scores for each patient visit were divided into 3 subgroups, with scores of 0 indicating no damage, scores of 1–2 moderate damage, and scores ≥ 3 severe damage. Similarly, for the distribution of SLEDAI scores over time, scores were divided into 3 groups, with a score of 0 (no disease activity), 1–10 (mild to moderate disease activity), and > 10 (severe disease activity). As SLEDAI scores fluctuate over time and to correct for variable disease durations, a weighted average of SLEDAI (WAS) was calculated for each patient to improve the estimated impact of disease activity on damage development and death. WAS designated the cumulative area under the observed SLEDAI curve, divided by the length of followup in months[37]. While several survival analysis models were constructed for various cutoff values of WAS, WAS scores > 3 not only gave the most consistent results but also corresponded to recommended cutoff levels for disease activity using SLEDAI[38].

Statistics. All figures represent median values (range) unless otherwise stated. Given the skewed distribution of most data, nonparametric test methods were used in data analysis. Numeric data were analyzed by Mann-Whitney U test, while dichotomized data were expressed as odds ratios (OR) with 95% confidence intervals (CI). Survival curves were estimated by the Kaplan-Meier method and compared by log-rank testing. Significant predictors for the relevant outcome were then entered into Cox regression models (p to enter < 0.1, p to stay < 0.05) to determine their independence. Resulting p values < 0.05 were considered statistically significant.

RESULTS

Damage accrual. After a mean followup of 11.9 years (median 10.2), 86 patients (54.4% of the study cohort, n = 158) had accrued damage (SDI ≥ 0; damage group). Compared to patients remaining free of damage [n = 72 (45.6%), last SDI = 0; no-damage group], they had significantly higher baseline SLEDAI scores and an increased prevalence of central nervous system (CNS) involvement (OR 13.8, 95% CI 1.9–108) and leukocytopenia (OR 2.2, 95% CI 1.2–4.1) at diagnosis (Table 1). Other demographics were not different between the 2 groups. The development of overall damage as a measure of time, expressed as the cumulative sum of patients in each SDI subgroup per followup year, showed a nearly continuous increase in the subgroups with DI scores ≥ 1 over a 10-year period, with subsequent flattening. The fraction of patients remaining free of damage diminished from 97% in the first year to 58% after 5 and 38% after 15 years (Figure 1A). In the damage group, mean damage scores at 1, 5, and 10 years for patients ≤ 40 years of age at diagnosis were 0.50 (median 0.0), 0.84 (median 1.0), and 0.97 (median 1.0), respectively, while they were 0.38 (median 0.0), 0.97 (median 0.5), and 1.23 (median 1.0) for patients > 40 years of age at diagnosis (p = 0.27, p = 0.84, and p = 0.64 for differences at 1, 5, and 10 years, respectively). The median last observed SDI in the total cohort was 1.26 (range 0–8), but within the damage group, it was 2.00 (mean 2.44, interquartile range 1–3). There was a strong correlation between followup time and damage accrual (Spearman coefficient R_s 0.37, p = 0.0001). Breakdown of the last recorded SDI into the different single-organ components (Figure 2) showed that most damage occurred in the musculoskeletal system (22.2%), followed by cardiovascular (17.8%), neuropsychiatric (15.2%), and peripheral vascular damage (11.39%).

Damage accrual as an outcome in relation to disease activity. In contrast to damage development the fraction of patient visits with high SLEDAI scores (> 10) was largest (14%) in the first year of disease and levelled off to 3–6% in the following years before decreasing to 0 after 15 years (Figure 1B). Meanwhile, the fraction of patient visits with mild to moderate disease activity (SLEDAI scores 1–10) also declined, from 48% in the first year to 33% after 10 years and 22% after 20 years' disease duration. Consequently, there was a large increase in the fraction of visits where no disease activity was detected. The absolute SLEDAI scores correlated negatively with followup time (R_s –0.27, p < 0.0001) and baseline SLEDAI was lower in patients remaining free of damage (Table 1). WAS (2.3 ± 2.9 vs 2.5 ± 2.5; p = 0.2) and mean cumulative SLEDAI scores (2.8 ± 2.7 vs 2.9 ± 2.3; p = 0.8) were comparable between the damage and no-damage group. Given the time-dependency of our outcome measures, survival analysis techniques were used to estimate the relative contribution of disease features to damage development. In univariate analysis, WAS > 3 was the only significant predictor of any damage accrual (endpoint last SDI score > 0; Table 2), while WAS > 3, initial SLEDAI > 10, male sex, and age > 40 years emerged as significant predictors (Table 2) for severe damage (endpoint last SDI ≥ 3). In the multivariate analysis, age > 40 years and WAS > 3 remained independent predictors for severe damage (Table 4).

Damage accrual in relation to disease activity as a predictor for mortality. Thirty-seven patients (23.4%) died during the observation period. The time of deaths in relation to disease duration demonstrated larger percentages of annual case fatalities in the second and third decade of disease (between 3% and 7%) than in the first decade (between 1% and 3%). Compared to surviving patients, nonsurvivors had higher last SDI scores (2.1 vs 0.9; p < 0.05) and higher levels of C-reac-

Table 1. Baseline demographics of the study cohort. Data are given for the whole cohort and for subgroups divided by damage development. Figures represent number of patients (%) or median values (range).

Feature	Total, n = 158	Last SDI = 0, n = 72 (45.6%)	Last SDI ≥ 1, n = 86 (54.4%)	p
Female/male	134/24 (85/15)	62/10 (86/14)	72/14 (84/16)	0.43
Caucasian	153 (96.8)	70 (46)	83 (54)	0.58
Age at diagnosis, yrs	36.5 (9–79)	33.0 (11–73)	39.8 (9–79)	0.11
Duration of disease, yrs	11.9 (0.5–38.6)	9.4 (0.5–27)	14.0 (0.5–39)	0.001
Symptomatic period before diagnosis, mo	19.9 (0–360)	17.1 (1–360)	24.5 (0–263)	0.58
SLEDAI score at inclusion	6.0 (0–30)	6.0 (0–28)	7.0 (0–30)	0.006
Renal disease	59 (37.3)	25 (35)	34 (40)	0.62
Arthritis	122 (77.2)	55 (76)	67 (78)	0.85
Malar rash	88 (55.7)	41 (57)	47 (55)	0.87
CNS involvement	15 (9.5)	1 (1.4)	14 (16)	0.002
Vasculitis	14 (8.9)	7 (10)	7 (8)	0.78
Serositis	54 (34.2)	22 (31)	32 (37)	0.40
Leukocytopenia	78 (49.4)	28 (39)	50 (58)	0.02
Thrombocytopenia	36 (22.8)	16 (22)	20 (23)	1.0
Anti-ds-DNA antibody-positive	85 (86.5)	42 (72)	43 (65)	0.44
Hypocomplementemia	43 (27.8)	23 (32)	21 (24)	0.37
Anti-Sm antibody-positive	20 (12.7)	11 (15)	9 (11)	0.47

p value for difference between patients with and without damage at last control. SLEDAI: SLE Disease Activity Index; CNS: central nervous system.

tive protein (36.8 vs 9.5 mg/dl; $p < 0.001$) and serum creatinine (144 vs 82 μmol/l; $p < 0.01$) at last observation, while last SLEDAI scores (2.4 vs 1.2; $p > 0.1$) did not differ. Nonsurviving patients had significantly higher rates of damage in the cardiovascular system (29.7% vs 14% in surviving patients), peripheral vascular tree (21.6% vs 8.3%), gastrointestinal system (16.2% vs 4.1%), and diabetes development (13.5% vs 4.1%) (all p values < 0.05). The independent contribution of demographics, SLEDAI measures, and SDI scores to patient survival was limited to WAS score > 3 (Tables 3 and 4).

DISCUSSION

In our study, more than half of all patients with SLE developed some organ damage within the first 10 years of disease, with severe damage occurring in a quarter of all patients. Damage accrual was in a linear fashion over the first 10 years, with apparent subsequent stabilization. Musculoskeletal damage was most frequent, followed by cardiovascular, neuropsychiatric, and peripheral vascular damage. The main risk factor for damage accrual was persistent disease activity over time, as indicated by increased WAS. Case fatalities were more frequent in the second and third decades of disease, and risk factors for death were WAS and age over 40 years at disease onset. Although nonsurviving patients had higher SDI scores, damage was not found to be an independent predictor of death.

The reported rate of patients with SLE who accrue damage was in almost complete accordance with other Scandinavian findings, where 46% of patients remained free of damage 5 years into the disease course[17]. The LUMINA study reported damage in 19% of Caucasian patients versus 39% in Hispanic and African American patients after 2 years[39], and 86% of Afro-Caribbean patients suffered damage after 6 years of followup[26]. Thus damage accrual is a function of race (although confounded by socioeconomic conditions) as well as a function of time, exemplified by the clear correlation between disease duration and SDI scores and the almost linear increases in rates of patients with damage over time (Figure 1A). Given this time-dependency and possibly to increase the applicability of SDI, it seems appropriate to incorporate a measure of time within the concept of overall SDI scores, such as annual damage increase rates. Interestingly, the relative stabilization of the number of patients with damage after 10 years indicates that it is not a certainty that damage will develop in all patients. There is also good evidence that "damage begets further damage" in SLE[27,32,29,40], indicating that a group of patients may remain free of damage and this group may provide important insights regarding patient management[41].

Musculoskeletal damage (seen in 23%) was also the most frequent damage seen in the Toronto cohort (29%), where it was related to prolonged disease duration[30]. In our study, cardiovascular damage (18%) was the second most frequent type of organ damage; the higher frequency compared to the Toronto cohort (11%) was likely due to their study of surviving patients only. The 12% musculoskeletal damage and 8% cardiovascular damage seen in Caucasian patients in the LUMINA cohort likely reflect their shorter followup[42].

The focus of our study was influence of disease activity measures during the disease course on damage development. Baseline SLEDAI scores > 10 were associated with damage

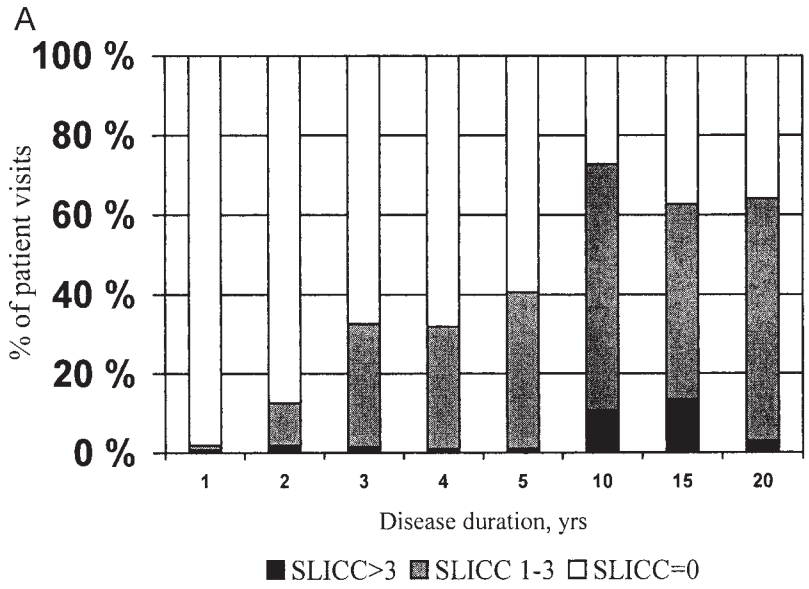

Figure 1A. Distribution of SDI scores over time in surviving patients. Actual figures may decrease over time due to varying total numbers of patients with the given followup time.

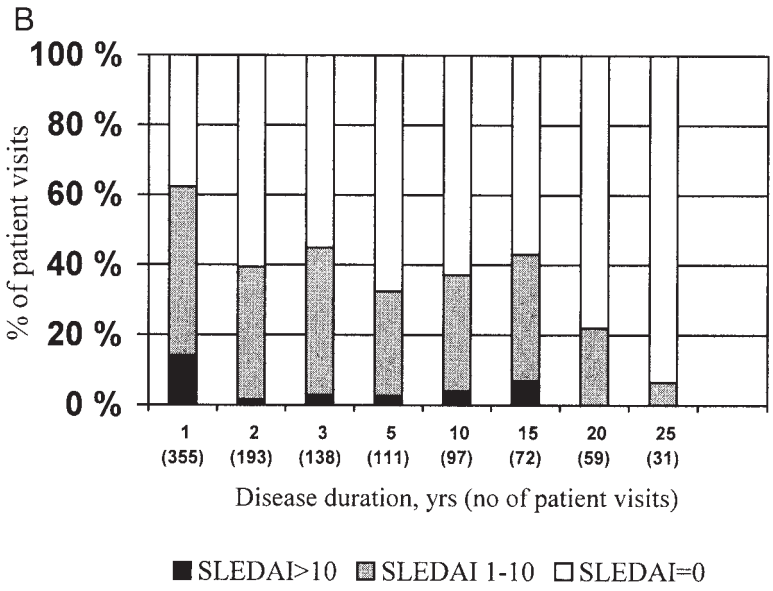

Figure 1B. Distribution of SLEDAI scores over time in surviving patients. Figures in parentheses denote number of patient visits in the respective year of disease duration.

development (Table 1) and when analyzed in univariate survival analysis (Table 2). In addition, baseline CNS involvement and leukocytopenia were associated with damage development, which corresponded to recent findings on damage in relation to neuropsychiatric lupus and specific autoantibody clustering[43,44]. However, no association existed with renal disease, anti-dsDNA antibody, and prednisone usage, as was seen in the LUMINA study; this was probably due to the lower rates of lupus nephritis in Nordic patients compared to non-Caucasian patients, while improved treatment modalities for lupus nephritis also may have contributed to this lack of association[31,35]. Despite these findings, the overall disease activity over time (WAS scores ≥ 3) was the sole overriding predictor of severe damage accrual in SLE. The importance of global disease activity over time[26,27,29] has now been described in cohorts of different ethnicities and serves as a clear reminder of the importance of achieving early clinical disease quiescence.

As in our study, higher SDI scores have been reported in nonsurviving patients, suggesting a prognostic role for dam-

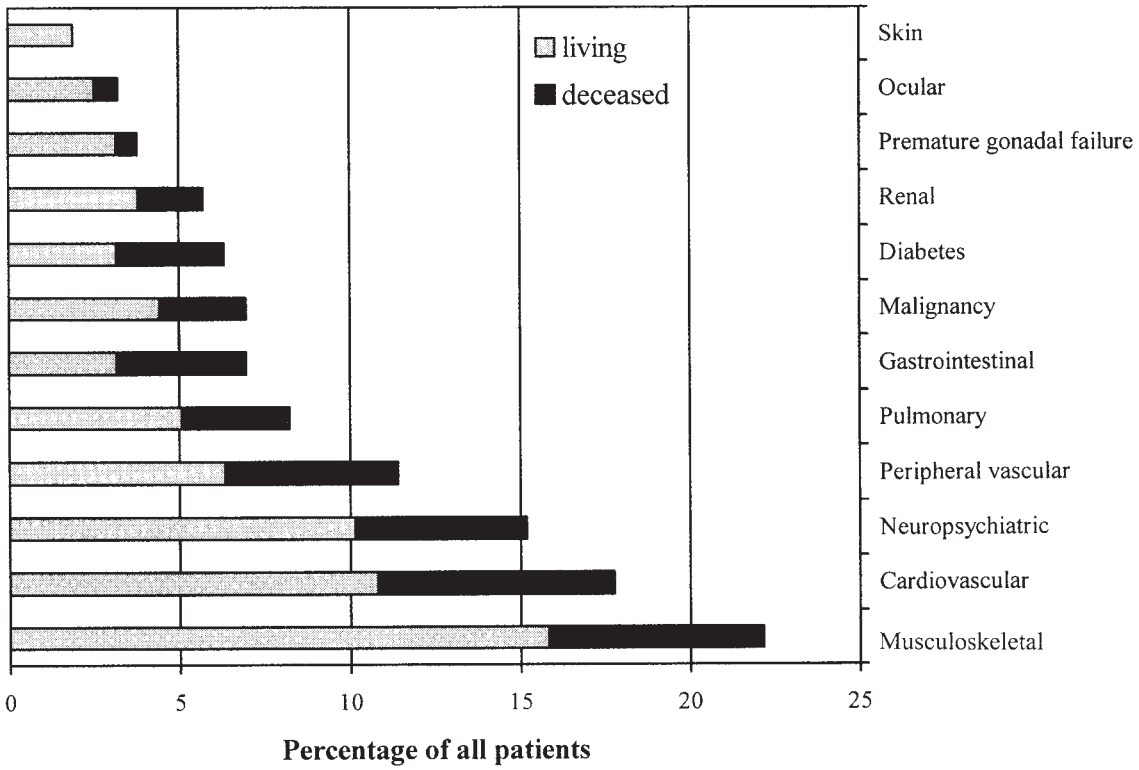

Figure 2. Frequencies of damage accrual at last visit in the various organ domains of the SLICC/DI. Figures represent percentages of the total cohort (n = 158).

Table 2. Univariate log-rank analysis of survival estimates for any damage (outcome SDI ≥ 1) and severe damage (SDI > 3).

	Last SDI = 0, n = 72	Last SDI ≥ 1, n = 86	Median Survival Time (95% CI)	p	Last SDI < 3, n = 122	Last SDI ≥ 3, n = 36	Median Survival Time (95% CI)	p
Age at diagnosis yrs								
≤ 40	47 (50.0)	47 (50.0)	12.4 (12.7–19.2)	0.07	78 (83.0)	16 (17.0)	35.7 (23.8–30.8)	0.0005
> 40	25 (39.1)	39 (60.9)	9.5 (8.6–13.3)		44 (68.8)	20 (31.3)	17.1 (14.1–19.0)	
Sex								
Male	11 (45.8)	13 (54.2)	6.8 (5.5–11.1)	0.14	17 (70.8)	7 (29.2)	17.7 (11.0–19.6)	0.02
Female	61 (45.5)	73 (54.5)	12.4 (12.1–17.2)		105 (78.4)	29 (21.6)	23.0 (22.0–28.0)	
Initial SLEDAI								
≤ 10	56 (46.7)	64 (53.3)	12.4 (12.2–17.8)	0.25	97 (80.8)	23 (19.2)	35.7 (22.7–29.3)	0.04
> 10	16 (42.1)	22 (57.9)	11.4 (7.9–15.6)		25 (65.8)	13 (34.2)	20.8 (14.8–21.7)	
WAS								
≤ 3	61 (49.2)	63 (50.8)	13.8 (12.3–18.3)	0.02	101 (81.5)	23 (18.5)	35.7 (22.9–29.6)	0.008
> 3	10 (29.4)	24 (70.6)	10.3 (6.3–13.3)		21 (61.8)	13 (38.2)	19.0 (14.0–22.1)	

WAS: Weighted average SLEDAI score.

age in lupus[11,17,18,45]. However, SDI was developed to provide an alternative for death as the outcome in SLE[46] and while it is intuitively attractive to use it as a predictor of death, there are few studies dealing with its prognostic value in detail. Although a significant univariate predictor, SDI was no longer predictive of death after adjusting for WAS scores and age (Table 4). This means that the deleterious effect of damage development is mediated through the combined negative effects of aging and disease activity on the reserve capacity of organ functions, a well recognized phenomenon in the loss of renal function in various other conditions[47].

Some limitations should be kept in mind with the interpretation of these findings. The government-sponsored Norwegian health system provides free healthcare to residents, including travel support to clinics. While approaching the ideal situation for patients with chronic conditions, it makes comparison with similar studies in otherwise paid-for health systems difficult. These single-center findings repre-

Table 3. Univariate (log-rank) analysis of patient survival estimates.

	Alive, n = 121	Dead, n = 37	Median Survival Time (95% CI)	p
Age, at diagnosis, yrs				
≤ 40	81 (86.2)	13 (13.8)	32.6 (26.2–33.4)	< 0.01
> 40	40 (62.5)	24 (37.5)	18.2 (14.0–19.0)	
Sex				
Male	16 (66.7)	8 (33.3)	15.6 (10.8–21.8)	0.03
Female	105 (78.4)	29 (21.6)	28.4 (22.8–29.4)	
SLEDAI at diagnosis				
≤ 10	95 (79.2)	25 (20.8)	32.6 (23.4–30.8)	0.3
> 10	26 (68.4)	12 (31.6)	28.4 (17.6–25.6)	
WAS				
≤ 3	102 (82.3)	22 (17.7)	32.6 (23.8–31.5)	0.01
> 3	19 (55.9)	15 (44.1)	22.8 (14.8–24.4)	
Last SDI				
0	59 (81.9)	13 (18.1)	27.0 (21.2–33.4)	0.65
≥ 1	62 (72.1)	24 (27.9)	29.9 (20.8–39.1)	
Last SDI				
< 3	101 (82.8)	21 (17.2)	26.3 (16.3–39.8)	0.42
≥ 3	20 (55.6)	16 (44.4)	28.4 (15.2–41.6)	

WAS: Weighted average SLEDAI score.

Table 4. Cox regression results of risk factors for death and severe damage development in SLE. Hazard ratios indicate the increase in likelihood that the outcome occurs for cases in the relevant category compared to cases in the opposite category. Data in bold type indicate the hazard ratios with independent prognostic value as their confidence intervals do not include 1.

	Death		Severe damage (SD ≥ 3)	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age > 40 at diagnosis	**5.57**	2.44–12.7	**3.45**	1.63–7.33
Male	1.45	0.6–3.4	1.8	0.71–4.54
Initial SLEDAI > 10	1.70	0.26–1.3	1.98	0.95–4.13
WAS > 3	**2.42**	1.19–4.92	**2.34**	1.13–4.81
SDI ≥ 3	1.44	0.67–3.09	NA	NA

sent data collected over a period up to 30 years in which changes in the availability and application of supportive therapies (such as antihypertensive treatment) have occurred, which may have biased our results. In addition, a shift in disease severity over this long period may have occurred, although there is presently no indication of this[3,48]. The use of total SDI scores can be criticized as an oversimplification, as damage in different organ systems may have different practical consequences. Individual organ damage scoring or weighing of SDI was not performed, as such approaches have not been successful before[13,49] and our use of condensed SDI scores (0 or higher and 3 or higher) avoids the problems with ordinal scales in SDI analysis. Further, SDI is a tool that has been in use for about one decade and was thus applied retrospectively to many patients in this cohort. However, good agreement exists between prospective versus retrospective evaluations of the total SDI scores as well as for interobserver and intraobserver variability[50]. Finally, our data concern patients fulfilling ACR criteria and cannot be extrapolated to patients with a clinical SLE diagnosis, who do not (yet) fulfil these criteria.

Damage development in patients with SLE occurred linearly over the decade of disease in a subset of patients. Damage accrual was dependent on global disease activity during the disease course. Persistent disease activity together with age over 40 years were the sole prognostic factors for death.

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