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Article

# Damage Accrual in Patients with Systemic Lupus Erythematosus Predicts Mortality and Is Associated Primarily with Antiphospholipid Syndrome and Hypertension

Short title: Damage Accrual in Patients with Lupus

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## Abstract

**Background/Objectives:** Irreversible organ damage is a central determinant of long-term outcomes in systemic lupus erythematosus (SLE). We aimed to define patterns of long-term damage accrual and identify dominant predictors of damage severity and mortality in a contemporary SLE cohort. **Methods:** This retrospective single-center study (2014-2023) included adult patients fulfilling 2019 EULAR/ACR SLE classification criteria. Damage was assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), at last follow-up and categorized as none (0), mild-moderate (1-2), or severe ( $\geq 3$ ). Various variables were assessed, including sociodemographic, disease-related characteristics, comorbidities, hospitalizations, emergency department visits, and all-cause mortality. Multivariable logistic regression and Cox models were applied. **Results:** Among 182 patients (84.1% female; mean follow-up 15.6 $\pm$ 11.4 years), 59.5% accrued damage, including 30.8% with severe damage. Damage predominantly involved cardiovascular, ocular, neuropsychiatric, and musculoskeletal domains. It was associated with older age, longer disease duration, hematologic and renal involvement, and corticosteroids and immunosuppressive medications. In multivariable analysis, antiphospholipid syndrome (APS) and hypertension emerged as the dominant independent predictors of damage accrual with an odds ratio of 15.70 (95% CI 4.26-57.89,  $p < 0.001$ ) and 6.46 (95% CI 2.54-16.40,  $p < 0.001$ ), respectively. Mortality increased with damage severity (16.1% in  $SDI \geq 3$ , 1.9% in  $SDI 1-2$ , none in  $SDI = 0$ ;  $p < 0.0001$ ). Damage was also associated with increased hospitalizations. **Conclusion:** Damage accrual is common and strongly predicts mortality. APS and hypertension emerge as dominant, modifiable drivers, supporting integrated cardiovascular and thrombotic risk management in SLE.

**Keywords:** systemic lupus erythematosus; damage accrual; antiphospholipid syndrome; hypertension; mortality

## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement and a highly heterogeneous clinical course [1]. Despite advances in diagnosis and management, patients with SLE continue to experience a mortality rate approximately twice that of the general population, with only modest improvement over recent decades [2]. One of the principal contributors to excess mortality and long-term morbidity in SLE is the accumulation of irreversible organ damage during the course of the disease. Patients with higher levels of damage are at a greater risk of premature death [3,4].

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (SDI) is a validated tool for measuring irreversible damage in patients with SLE. SDI items capture irreversible damage occurring after the diagnosis of SLE, irrespective of attribution [4,5]. Damage accrual has consistently been shown to predict adverse outcomes, including hospitalization, impaired quality of life, and premature mortality. Given the prognostic significance of damage accrual, current recommendations for the management of SLE emphasize damage prevention as a central therapeutic goal and stress the importance of assessing damage regularly [6,7].

Established contributors to damage include cumulative disease activity, recurrent flares, comorbid conditions such as hypertension and antiphospholipid syndrome (APS), and treatment-related factors, particularly prolonged glucocorticoid exposure. Importantly, the burden and pattern of damage accrual vary across populations and geographic regions, influenced by ethnicity, socioeconomic factors, disease phenotype, and healthcare access [4,5,8,9].

This study aimed to characterize long-term organ damage accrual in a contemporary Israeli SLE cohort and to identify clinical and comorbidity-related factors associated with damage presence, severity, and adverse outcomes, including mortality.

## 2. Materials and Methods

### 2.1. Study Design and Population

This retrospective, single-center study was conducted at Meir Medical Center (MMC). MMC is a 795-bed academic hospital in the Sharon district in central Israel with inpatient and outpatient services. It is the district's largest hospital, serving a predominantly urban population consisting of both Jews and Arabs. This study utilized data from the Medical Center's electronic medical records (EMR), which contains comprehensive medical information from ambulatory clinics, the emergency room, and hospital departments that is accessible at the individual patient level. The database includes all diagnoses, demographic, clinical data, and laboratory values.

The study population consisted of SLE patients aged 18 years or older, diagnosed for at least 12 months, who were treated at MMC between January 1, 2014, and December 31, 2023. Patients were required to fulfill the 2019 EULAR/ACR Classification Criteria for SLE, to be included. All medical records were reviewed by a rheumatologist (OETS) to confirm the diagnosis of SLE.

### 2.2. Measured Outcomes

Damage was measured at the last follow-up using the SDI. Patients were categorized into three groups according to the severity of damage: no damage (SDI 0), mild-moderate damage (SDI 1-2), and severe damage (SDI  $\geq 3$ ). Socioeconomic status was defined using the municipal socioeconomic index from the Central Bureau of Statistics. Comorbidities such as diabetes mellitus, hypertension and cardiovascular disease (including ischemic heart disease, stroke and heart failure) were defined by diagnosis in the EMR at any time during follow-up. The number of patients with emergent hospitalizations was recorded and categorized according to hospitalization cause: SLE exacerbation, infection, or cardiovascular event. All-cause mortality data were collected using the national data center, including in-hospital and home deaths. Additional demographic, clinical, and laboratory data, including SLE treatments, were recorded and analyzed.

### 2.3. Statistical Analysis

Descriptive data are presented as mean  $\pm$  standard deviation (SD) for continuous variables and as numbers and percentages for non-metric parameters. Chi-squared test was used to compare categorical parameters and t-test was applied for continuous variables comparison. A p-value  $<0.05$  was considered statistically significant.

Multivariate logistic regression analysis was used for assessing predictors of damage. A multivariable Cox proportional hazards model was constructed to obtain covariate-adjusted measures of survival.

All statistical analyses were performed using SPSS Version 29 (IBM Corporation, Armonk, NY, USA).

## 3. Results

### 3.1. Patients' Characteristics

A total of 182 patients were followed for a mean duration of  $15.6 \pm 11.4$  years. Of these, 84.1% were female, 74.7% were Jewish, and 22.5% were Arab. Socioeconomic status was categorized as high in 48.1% of patients and low in 15.5% (Table 1). Hydroxychloroquine was used at some point during the disease course in 98.3% of patients; data regarding its use were missing for the remaining 1.65%. The most prevalent comorbidities at the end of follow-up were hypertension (32.4%) and APS (23.6%). Additionally, 9.9% of patients had diabetes mellitus (DM), and 10.4% had cardiovascular disease (CVD) (Table 1).

**Table 1.** Demographic and clinical characteristics of patients according to the severity of damage.

	No damage (SDI 0) N=73	Mild- moderate damage (SDI 1-2) N=53	Severe damage (SDI $\geq$ 3) N=56	Total N=182	p-value
<b>Female sex, n (%)</b>	64 (87.7%)	43 (81.1%)	46 (82.1%)	153 (84.1%)	NS
<b>Age at last follow-up, years, mean <math>\pm</math> SD</b>	39.85 $\pm$ 13.03	48.89 $\pm$ 14.96	59.18 $\pm$ 16.02	48.43 $\pm$ 16.59	$<0.0001$
<b>Age at diagnosis, years, mean <math>\pm</math> SD</b>	31.12 $\pm$ 14.30	34.86 $\pm$ 12.69	34.70 $\pm$ 16.00	33.3 $\pm$ 14.40	NS
<b>Ethnicity, n (%)</b>					
Jewish	58 (79.5%)	39 (73.6%)	39 (69.6%)	136 (74.7%)	NS
Arab	12 (16.4%)	12 (22.6%)	17 (30.4%)	41 (22.5%)	
Other	3 (4.1%)	2 (3.8%)	0 (0.0%)	5 (2.7%)	
<b>Socioeconomic status<sup>†</sup>, n (%)</b>					
Low (1-3)	6 (8.2%)	9 (17.0%)	13 (23.7%)	28 (15.5%)	NS
Medium (4-7)	27 (37.0%)	22 (41.5%)	17 (30.9%)	66 (36.5%)	
High (8-10)	40 (43.7%)	22 (41.5%)	25 (45.4%)	87 (48.1%)	
<b>SDI score, mean <math>\pm</math> SD</b>	0.0 $\pm$ 0.0	1.41 $\pm$ 0.59	0.6 $\pm$ 0.29	1.41 $\pm$ 0.59	$<0.0001$
<b>EULAR/ACR criteria cumulative score, mean <math>\pm</math> SD</b>	20.78 $\pm$ 9.03	21.87 $\pm$ 7.50	25.27 $\pm$ 9.01	22.46 $\pm$ 8.77	0.013
<b>Comorbidities</b>					
APS, n (%)	3 (4.1%)	15 (28.3%)	56 (44.6%)	43 (23.6%)	$<0.0001$
HTN, n (%)	8 (11.0%)	15 (28.3%)	36 (64.3%)	59 (32.4%)	$<0.0001$
<b>Systolic BP last, mmHg, mean <math>\pm</math> SD</b>	122.9 $\pm$ 20.6	123.4 $\pm$ 16.7	134.1 $\pm$ 22.3	126.9 $\pm$ 20.7	0.007

Diastolic BP last, mmHg, mean $\pm$ SD	71.9 $\pm$ 12.8	73.9 $\pm$ 10.9	78.0 $\pm$ 12.1	74.6 $\pm$ 12.2	0.031
ESRD, n (%)	0 (0.0%)	0 (0.0%)	9 (16.1%)	9 (4.9%)	<0.0001
DM, n (%)	3 (4.1%)	2 (3.8%)	13 (23.2%)	18 (9.9%)	<0.0001
CVD, n (%)	0 (0.0%)	6 (11.3%)	13 (23.2%)	19 (10.4%)	<0.0001
<b>Laboratory:</b>					
Low C3 and/or C4 ever, n (%)	49 (67.12%)	36 (67.92%)	41 (73.12%)	126 (69.23)	NS
Positive anti dsDNA ever, n (%)	51 (69.9%)	43 (81.1%)	44 (78.6%)	138 (75.8%)	NS
Lymph. min., K/microL, mean $\pm$ SD	1.18 $\pm$ 0.71	1.03 $\pm$ 0.68	0.74 $\pm$ 0.61	0.99 $\pm$ 0.69	0.003
HGB min., g/dL, mean $\pm$ SD	11.39 $\pm$ 1.64	10.70 $\pm$ 2.24	9.22 $\pm$ 2.08	10.45 $\pm$ 2.18	<0.0001
PLT min., K/microL, mean $\pm$ SD	186.00 $\pm$ 73.53	172.87 $\pm$ 60.05	133.75 $\pm$ 65.63	164.38 $\pm$ 70.43	<0.0001
eGFR, last, ml/min, mean $\pm$ SD	115.94 $\pm$ 35.01	99.27 $\pm$ 34.33	64.43 $\pm$ 45.39	93.53 $\pm$ 44.30	<0.0001
<b>Medications, n (%):</b>					
HCQ, n (%)	57 (78.1%)	43 (81.1%)	31 (55.4%)	131 (72.0%)	NS
GCS, ever, n (%)	49 (67.1%)	44 (83.0%)	51 (91.1%)	144 (79.1%)	0.001
GCS dosage*, mean $\pm$ SD	1.73 $\pm$ 3.33	2.36 $\pm$ 3.69	4.43 $\pm$ 5.66	2.75 $\pm$ 4.40	0.002
Immunosuppression, ever, n (%)	19 (26.0%)	17 (32.1%)	20 (35.7%)	56 (30.8%)	0.005
Belimumab, ever, n (%)	14 (19.2%)	14 (26.4%)	13 (23.2%)	41 (22.5%)	NS
<b>Outcomes</b>					
Mortality, n (%)	0 (0.0%)	1 (1.9%)	9 (16.1%)	10 (5.5%)	<0.0001
ED visits per patient, mean $\pm$ SD	3.22 $\pm$ 5.06	4.46 $\pm$ 5.10	8.35 $\pm$ 9.13	5.16 $\pm$ 6.89	<0.0001
Hospitalizations: SLE exacerbation, n (%)	13 (19.7%)	11 (22.9%)	24 (46.2%)	48 (28.9%)	0.004
Severe infection, n (%)	8 (12.1%)	11 (22.9%)	27 (51.9%)	46 (27.7%)	<0.0001
CVE, n (%)	1 (1.5%)	11 (22.9%)	15 (28.8%)	27 (16.3%)	<0.0001

**All variables measured at last follow-up unless stated otherwise.** SDI: Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index; EULAR: European Alliance of Associations for Rheumatology; ACR: American College of Rheumatology; APS: antiphospholipid syndrome; HTN: hypertension; BP: blood pressure; ESRD: end-stage renal disease; DM: diabetes mellitus; CVD: cardiovascular disease including stroke, congestive heart failure and ischemic heart disease; lymph.: lymphocytes count; HGB: hemoglobin; PLT: platelets; min.: minimum value; eGFR: estimated glomerular filtration rate; HCQ: hydroxychloroquine; GCS: glucocorticosteroids; CYC: cyclophosphamide; MMF: mycophenolate mofetil or mycophenolic acid; ED: emergency department; SLE: systemic lupus erythematosus; CVE: cardiovascular event. <sup>¶</sup>Socioeconomic status was defined according to the municipal socio-economic index by the Central Bureau of Statistics. \*Corticosteroids dosage of prednisone or prednisone equivalent.

### 3.2. Prevalence of Damage Accrual

Damage had occurred in 59.5% of the cohort (109 patients). Of them, 53 (48.6%) had mild to moderate damage, and 56 (51.4%) had severe damage (Figure 1). The mean SDI score was  $1.88 \pm 2.34$ . The most commonly affected SDI domains were cardiovascular (29.7%), ocular (26.9%), neuropsychiatric (23.1%), and musculoskeletal (21.9%) (Figure 2).

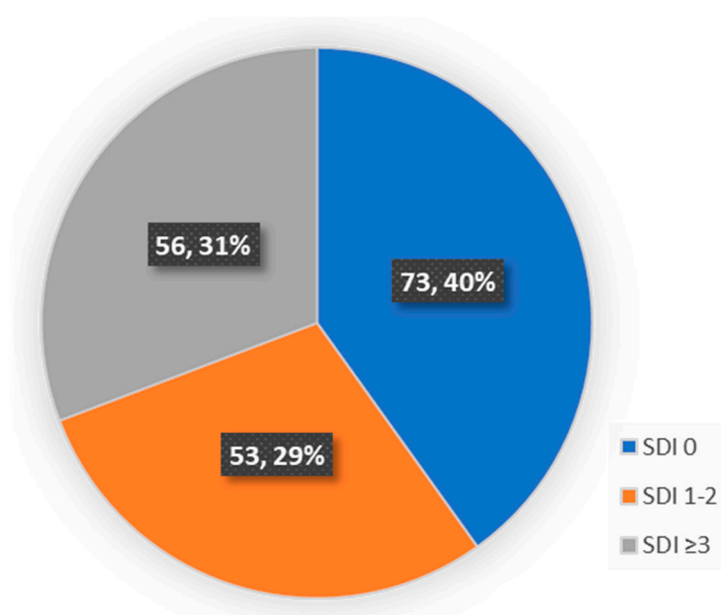


Figure 1.

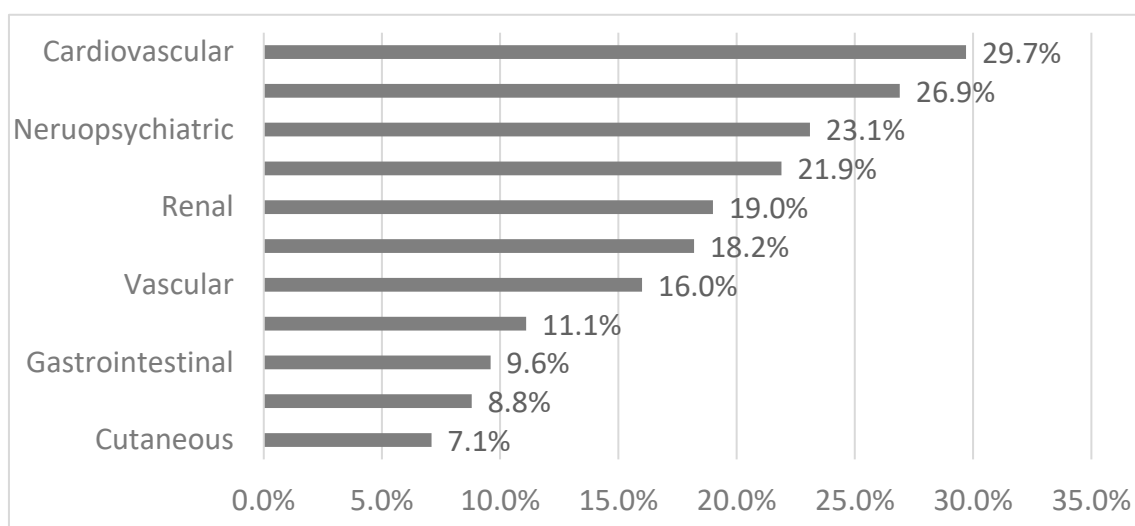


Figure 2.

### 3.3. Factors Associated with Damage Accrual

Patients with damage were older, had a longer follow-up, had higher cumulative EULAR/ACR criteria scores, and exhibited more frequent hematologic and renal involvement. These factors were associated not only with damage accrual but also with its severity (Table 1). Comorbidities, including hypertension, diabetes, cardiovascular disease, end-stage renal disease, and APS were significantly associated with damage accrual. Damage accrual was also associated with lower hemoglobin levels, lymphopenia, and thrombocytopenia.

The use of corticosteroids and immunosuppressives at any time was associated with damage accrual, as well as with mean glucocorticoid dosage at last follow-up, but no association was found with the use of belimumab.

Although the severe damage group included a larger proportion of Arab patients and those from a lower socioeconomic status, neither socioeconomic status nor ethnicity (Jewish/Arab) was statistically significant (Table 1).

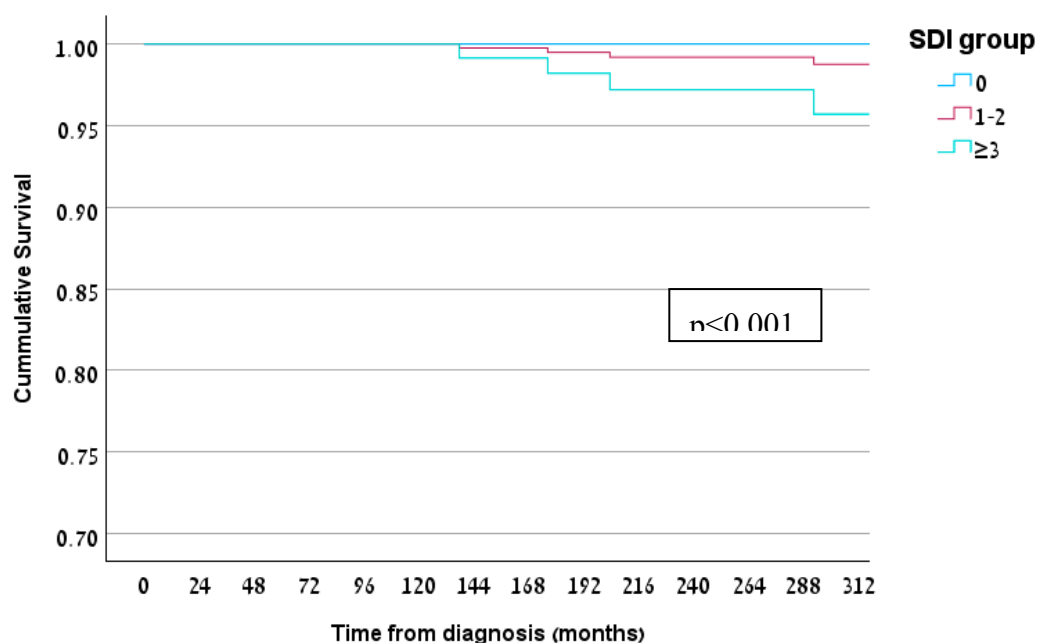
### 3.4. Multivariable Analysis and Outcomes

In the multivariable regression analysis model, APS and hypertension emerged as the strongest independent predictors of damage accrual (Table 2).

**Table 2.** Multivariable analysis for predictors of damage.

	Odds ratio	95% CI		P value
		lower	upper	
Sex	0.512	0.188	1.391	0.189
Age at diagnosis	1.004	0.977	1.032	0.787
Ethnicity	1.351	0.547	3.337	0.515
<b>Hypertension</b>	<b>6.460</b>	<b>2.544</b>	<b>16.399</b>	<b>&lt;0.001</b>
<b>Antiphospholipid syndrome</b>	<b>15.704</b>	<b>4.260</b>	<b>57.891</b>	<b>&lt;0.001</b>
Depression	1.734	0.417	7.216	0.449
Anxiety	1.191	0.312	4.543	0.798

Mortality occurred in 16.1% of patients with SDI  $\geq 3$ , compared with 1.9% in the SDI 1–2 group and no deaths in patients without damage ( $p < 0.0001$ ) (Table 1, Figure 3). Damage was also associated with hospitalizations for severe infections, SLE flares, and emergency department visits (Table 1).



**Figure 3.** Age- and sex-adjusted Cox survival model according to SDI group. SDI: Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index.

## 4. Discussion

In this long-term, single-center Israeli cohort, irreversible organ damage was observed in nearly 60% of patients with SLE after a mean follow-up of over 15 years. Damage accrual was strongly associated with adverse clinical outcomes, including hospitalization and mortality, reinforcing the central role of damage prevention in contemporary SLE management. Multivariable analysis demonstrated that APS and hypertension were the strongest independent predictors of damage accrual.

The prevalence and severity of damage observed in our cohort are within the range reported in previous reports from Israel and international cohorts. A prior study in Israel by Molad et al. [10]

reported a comparable damage rate of 61.6%, with a mean SDI of  $1.64 \pm 2.1$ , despite a considerably shorter mean follow-up of  $3.8 \pm 3.12$  years. Since damage accrual in SLE is known to increase progressively over time [3], the similarity in mean SDI scores between our longer-term study and Molad's earlier cohort is notable and may reflect differences in cohort characteristics, management strategies, or disease severity. However, our findings align with global data: the SLICC Inception Cohort [4] reported that 51.1% of patients had accrued at least one item of damage within six years of clinic entry. Likewise, studies from Brazil [11] and China [8] reported damage accrual rates of 55% and 42.8%, respectively. Collectively, these observations underscore the substantial global burden of irreversible organ damage in SLE and highlight the SDI as a reliable, cross-contextual measure for long-term outcomes in diverse patient populations.

The pattern of organ involvement, predominantly cardiovascular, ocular, neuropsychiatric, and musculoskeletal, mirrors findings from both the SLICC inception cohort and earlier Israeli studies, [3,10–12]. There were higher rates of renal damage in some cohorts, mostly in non-Caucasian populations [8,11], that may reflect ethnic differences in disease phenotype and severity. Notably, we observed a higher prevalence of musculoskeletal damage than in the earlier Israeli cohort by Molad et al. [10], which aligns with Gladman et al.'s observation that musculoskeletal damage frequently emerges as a late complication, typically after five years of disease [3]. Overall, our findings support a shared profile of organ damage in SLE, largely independent of geographic or ethnic background, while also highlighting some potential variations in domain-specific damage prevalence.

APS emerged as the most powerful independent predictor of damage accrual, conferring a markedly increased risk of severe irreversible organ damage. Nearly half of patients with severe damage had concomitant APS, compared with 4% of patients with no damage, underscoring the profound impact of thrombo-inflammatory mechanisms on long-term outcomes in SLE. Prior studies on the association between antiphospholipid antibodies (aPL) or APS and damage accrual in patients with SLE reported heterogeneous and sometimes inconsistent results. Multiple studies support the association between APS and increased damage in SLE, particularly involving neuropsychiatric and cardiovascular domains. Studies have demonstrated that SLE-APS patients accumulate more extensive and progressive damage over time and have higher mortality rates. Notably, these effects appear to exceed those seen in patients with primary APS, SLE without APS, or SLE with isolated aPL positivity without APS, suggesting a synergistic burden in the context of coexisting SLE [13,14]. The high odds observed in our cohort further emphasize the need for vigilant screening, early recognition, and aggressive intervention in patients with APS, particularly those with concurrent hypertension or multiorgan involvement. Integrating APS management into routine SLE care may be essential to reducing irreversible damage and improving long-term outcomes.

Hypertension was the second strongest independent predictor of damage accrual in our cohort. Hypertension is highly prevalent among patients with SLE and occurs more frequently than in the general population. It represents a major, modifiable driver of cardiovascular disease and renal damage, both of which are leading contributors to long-term morbidity in SLE [15]. Prior study have also identified hypertension, alongside corticosteroid use and age, as an independent determinant of damage accrual in SLE [5].

Contrary to previous reports, socioeconomic status and ethnicity were not significantly associated with damage accrual in our cohort, although there was a numerical difference. This finding contrasts with previous studies [5,16], including a study from Israel by Sagy et al. [17], which have demonstrated that low socioeconomic status is significantly associated with poorer outcomes in SLE patients, even within healthcare systems that provide universal coverage. This finding may reflect the centralized location of our medical center, together with Israel's universal healthcare system, which may alleviate disparities in access to specialized care and advanced therapies.

The strong association between damage severity and mortality observed in this study further confirms the prognostic significance of the SDI [18]. Importantly, no deaths occurred among patients without damage, emphasizing damage accrual as a critical inflection point in long-term SLE outcomes. Prior cohort and meta-analyses have consistently shown that irreversible organ damage

independently predicts mortality in SLE, with each 1-point increase in SDI associated with a pooled HR of 1.34 risk of death [19]. Damage involving renal, cardiovascular, neuropsychiatric, and musculoskeletal systems has been particularly linked to increased mortality [20]. These findings underscore the importance of preventing damage accrual through optimal disease control and early targeted intervention to improve long-term survival.

This study has limitations inherent to its retrospective, single-center design, including incomplete data on disease activity and treatment exposure over time. Additionally, while the study includes a diverse population in Israel, the findings cannot be generalized to other populations. Nevertheless, its strengths include a long follow-up period, comprehensive clinical data on SLE damage accrual, and inclusion of a diverse Israeli population adding valuable insight into long-term disease management.

## 5. Conclusions

Damage accrual remains a major determinant of morbidity and mortality in SLE. Our findings underscore the importance of integrating aggressive management of comorbid conditions, such as APS and hypertension, alongside disease-directed therapies to prevent irreversible organ damage. Prospective studies are needed to evaluate targeted interventions aimed at high-risk patients and to refine strategies for long-term damage prevention.

**Author Contributions:** Conceptualization: OETS, KCH and SK; methodology: OETS, KCH and IS; formal analysis: OETS and KCH; investigation: YPB, HHP, DE, and IS; data curation: YPB and HHP; writing-original draft preparation, YPB and OETS; writing-review and editing, all authors; supervision, OETS. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** The data presented in this study are available from the corresponding author upon reasonable request.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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