Rate and predictors of chronic organ damage accrual in active lupus nephritis: a single centre experience over 18 years of observation

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Abstract

Objective

We aimed to identify the rates and predictors of chronic damage accrual and mortality in lupus nephritis (LN).

Methods

We retrospectively measured SLICC/ACR Damage Index (SDI) in biopsy proven active LN with at least 5 years follow-up. We searched for the predictors of first SDI increase and death at univariate and multivariate regression analysis. Then, we considered clinical/biochemical/histological features at diagnosis, corticosteroids dose and proportion of follow-up in complete renal remission.

Results

187 patients (91.4% females, age 28.1 years, 95.7% Caucasians) were included. After a median follow-up of 18.6 years, 26 patients (13.9%) died, 116 (62%) accrued damage. SDI annual rate has significantly reduced over the last decades (from a mean of 0.14±0.17 in 1970–1985, to 0.09±0.21 in 1986–2001, to 0.07±0.1 in 2002–2019; p=0.0032). SDI increases occurred more frequently in renal (22.5%), ocular (18.2%), cardiovascular, neuropsychiatric (13.4% both) and malignancy (12.8%) domains. First SDI increase free survival was 73.3%, 59.8%, 49.9% and 38% at 5,10,15 and 20 years. At multivariate analysis, hypertension (HR:1.699, CI:1.126–2.457, p=0.011), presentation with acute renal dysfunction (HR:1.587,CI:1.082–2.327, p=0.018) and average prednisone dose >5mg/day (HR:3.378, CI:1.984-5.751, p<0.0001) independently predicted damage. Achievement of complete renal remission (HR:0.993, CI:0.987–0.999, p<0.039) reduced the risk of damage. Age (HR:1.063, CI:1.027–1.099, p=0.0004), hypertension (HR:3.096, CI:1.211–7.912, p=0.019), and no immunosuppressors as maintenance therapy (HR:4.168, CI:1.212–14.336, p=0.024) predicted mortality at multivariate analysis.

Conclusion

Besides arterial hypertension, presentation with acute renal dysfunction and corticosteroids dose predict SDI increase in LN, while achieving renal remission prevents damage. Aggressive therapy to induce remission in the acute phases of LN and low corticosteroids dose in maintenance therapy may prevent the increase of chronic damage.

Key words

systemic lupus erythematosus, lupus nephritis, chronic organ damage, SLICC/ACR Damage Index, mortality

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Introduction

Over the last decades, the progressive improvement of standard of care and supportive therapies has turned systemic lupus erythematosus (SLE) from being a fatal disease into a chronic condition (1, 2). Despite improved short-term survival, irreversible organ damage accrues gradually during the course of the disease (3), contributes to impaired health-related quality of life (4) and causes increased long-term mortality (3, 5, 6). Indeed, recent data have shown that SLE patients' mortality has not improved in recent years, remaining more than double than in general population (7).

Organ damage is measured with the SLICC/ACR Damage Index (SDI). Several registries reported data about the value of SDI in SLE during the last 20 years (8-20). It emerges that SDI is a validated instrument to measure irreversible damage in SLE patients (8). To improve SLE outcome, the identification of predictors of damage accrual is of great importance. Several predictors of SDI increase have been identified in SLE patients. In addition to SLE activity (9, 10) and its treatment (11, 12), pre-existing organ damage at diagnosis predicts further damage (13). Previous cohort studies, including SLE patients with any organ involvement, identified in disease duration (14), male gender (15), age at onset (16), non-Caucasian ethnicity (17), occurrence of flares (18) and arterial hypertension (19) the predictors of SDI accrual. In contrast, use of antimalarials seems to protect from damage accrual (3, 19, 20).

Few data are available about SDI increase in patients with lupus nephritis (LN), that is one of the most severe complications of SLE (21, 22). Despite progressive improvement on survival observed during the last fifty years, LN carries higher risk of mortality and morbidity in comparison to SLE without kidney involvement (23). For these reasons, the identification of predictors of SDI increase in LN may suggest interventions able to reduce the progression of damage over time.

In this study, we applied SDI to evaluate the rate of development of damage accrual in a biopsy proven cohort of active LN patients followed in our Renal Unit for at least five years. We looked for the predictors of increase in SDI score and mortality at univariate and at multivariate regression analysis, testing the features at diagnosis of LN, the corticosteroids dosage and the proportion of follow-up spent in complete renal remission.

Material and methods

Study cohort

Patients, aged older than 16 years, followed in our Renal Unit (Fondazione IRCCS Ca' Granda Ospedale Maggiore Milano), who had a biopsy-proven active LN and a follow-up of at least five years after diagnosis of LN, were included in this retrospective analysis of prospectively collected data.

Inclusion criteria were: i) SLE patients classified according to ACR criteria (24); ii) active LN based on clinical and renal biopsy data, diagnosed between January 1970 and December 2014; iii) at least two clinical and laboratory assessments per year during the follow-up. Exclusion criteria were the presence of damage in SDI renal domains at inclusion in the study.

The study was approved by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Italy (protocol number 505_2019bis). All patients signed an informed consent for the scientific use of their data at the time of renal biopsy.

Patients' assessment

In 2005 we collected in a database the demographics, clinical, laboratory and therapeutic variables (reported in Table I) at baseline and at each clinical evaluation of patients with LN diagnosed since 1970. The database was regularly updated with the new cases until December 2019.

We considered as baseline of the study the start of induction therapy soon after the histologic diagnosis of LN and, the end of the observation December 2019, or the data of death. Renal biopsies were classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria (25) and assessed in terms of chronicity and activity indexes according to Aus-

Table I. Characteristics of all patients and comparison between those with and without first SDI increase.

	All 187 patients	SDI unchanged 71 patients	SDI increase ≥1 116 patients	*p*-value
Baseline characteristics				
Female, n (%)	171 (91.4)	65 (91.5)	106 (91.7)	0.968
SLE duration, years	0.3 (0-4.2)	1 (0-7.1)	0.1 (0-2.4)	**0.006**
Age at SLE diagnosis, years	25 (19.7-33.8)	22.9 (17.3-21.5)	25.8 (20.9-34.4)	**0.024**
Age at LN diagnosis, years	28.1 (21.9-37.8)	27.4 (21.1-37.1)	28.4 (22.4-39.2)	0.410
Diagnosis of LN before 2000, n (%)	119 (63.6%)	33 (46.5)	86 (74.1)	**0.0001**
Serum creatinine >1mg/dl, n (%)	76 (40.6)	17 (23.9)	59 (50.9)	**0.008**
eGFR <60 ml/min/1.73mq	59 (31.6)	12 (16.9)	47 (40.5)	**0.0007**
Proteinuria g/24h	3.6 (1.8-5.3)	2.6 (1.4-4.7)	4 (2.1-5.7)	**0.005**
Arterial hypertension, n (%)	93 (49.7)	22 (31)	71 (61.2)	**0.0009**
Anti-hypertensive monotherapy, n (%)	47 (50.5%)	8 (36.4)	39 (54.9)	0.128
ACEi/ARBs 36				
Others* 11				
Anti-hypertensive polytherapy	46 (49.5%)	14 (63.6)	32 (45.1)	0.128
ACEi/ARBs + others* 42				
Others* 4				
Acute renal dysfunction, n (%) [a]	58 (31)	12 (16.9)	46 (39.7)	**0.001**
Serum albumin, mg/dl	2.9 (2.3-3.5)	3.1 (2.6-3.6)	2.7 (2.3-3.3)	**0.005**
C3, mg/dl	58 (49-78.5)	62 (47-80.5)	56 (49.8-74.3)	0.617
C4, mg/dl	11 (6-16)	11.3 (7-16.8)	10 (6-15)	0.426
APL Ab, n (%)	39 (20.9)	13 (18.3)	26 (22.4)	0.503
Histological class II+V *vs*. III+IIV, n (%)	45 (24.6), 142 (75.4)	21 (29.6) / 50 (70.4)	24 (20.7) / 92 (79.3)	0.168
Activity index	6 (3-9)	5 (2-8)	6 (3-9.3)	0.062
Chronicity index >1, n (%)	85 (45.5)	26 (36.6)	59 (50.9)	**0.045**
SDI basal mean (DS)	(± 0.4)	(± 0.4)	0.1 (±0.4)	0.124
SDI >0, n (%)	16 (8.6)	9 (12.7)	7 (6)	0.115
SLEDAI	15 (10.5-19)	14 (10-17.5)	15.5 (11.8-19)	0.139
Induction with MP pulses, n (%)	143 (76.5)	60 (84.5)	83 (71.6)	0.062
Induction with IS, n (%)	145 (77.5)	58 (81.7)	87 (75)	0.287
CYC, n (%)	96 (51.3)	36 (50.7)	60 (51.7)	0.892
MMF, AZA, CsA, MTX, RTX n (%)	18 (9.6), 20 (10.7), 5 (2.7), 3 (1.6), 3 (1.6)	12 (16.9), 5 (7.1), 2 (2.8), 2 (2.8), 1 (1.4)	6 (5.2), 15 (12.9), 3 (2.6), 1 (0.9), 2 (1.7)	**0.008**, 0.206, 0.924, 0.302, 0.867
Hydroxychloroquine, n (%)	101 (54)	51 (71.8)	50 (43.1)	**0.0001**
Characteristics from LN diagnosis to the first SDI increase				
Maintenance therapy with IS, n (%)	89 (47.6)	43 (60.6)	46 (39.7)	**0.005**
AZA, MMF, CsA, n (%)	42 (22.5), 37 (19.8), 10 (5.3)	15 (21.1), 23 (32.4), 5 (7.1)	27 (23.4), 14 (12.1), 5 (4.3)	0.732, **0.0007,** 0.420
Cumulative average PDN dose mg/day	7.1 (4.7-10.8)	5.1 (3.2-6.9)	9.3 (6.5-14.5)	**<0.0001**
Cumulative average PDN >5 mg/day, n (%)	132 (70.6)	36 (50.7)	96 (82.7)	**<0.0001**
% of follow-up spent in complete renal remission	47 (13.8-75.4)	63.9 (32.8-84)	40.9 (0-56.8)	**<0.0001**
≥40% of follow-up spent in complete renal remission, n (%)	111 (59.4)	52 (73.2)	59 (50.9)	**0.002**

SLE: systemic lupus erythematosus; LN: lupus nephritis; eGFR: estimated glomerular filtration rate; ACEi/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; APL Ab: antiphospholipid antibodies; MP: methylprednisolone; SDI: SLICC Damage Index; SLEDAI: systemic lupus erythematosus disease activity index; IS: immunosuppressors; CYC: cyclophosphamide; MMF: mycophenolate mofetil; AZA: azathioprine; CsA: cyclosporine A; MTX: methotrexate; RTX: rituximab; PDN: prednisone;

[a] acute renal dysfunction includes 47 patients with acute nephritic syndrome and 11 with rapidly progressive renal insufficiency. Unless differently specified, the data are reported as median and interquartile ranges.

*Calcium channel blockers, beta-blockers.

tin *et al*. (26). After renal biopsy, all patients were followed by a dedicated team in our Unit. They were evaluated one month after the start of therapy, then every 2–3 months, until one year, and then every 3–6 months thereafter.

Organ damage was assessed once a year at the study visit using the SDI score (8).

Definition of renal variables

Clinical presentation of LN was classified as (27)*:*

Acute renal dysfunction: serum creatinine >1 mg/dl and eGFR ≤60ml/min/1.73m^2 that includes: acute nephritic syndrome: macroscopic or severe microscopic haematuria (urinary red blood cells >20/HPF), and/or erythrocytes casts, arterial hypertension and variables degrees of proteinuria >0.5g/24 hours*)* and rapidly progressive renal insufficiency: rapid deterioration of renal function leading to chronic kidney disease (CKD) stage 3 to 5 within a few weeks, with oliguria, arterial hypertension and severe haematuria.

Normal renal function: serum creatinine ≤1mg/dl and estimated glomerular filtration rate (eGFR)>60ml/min/1.73m^2 that includes: urinary abnormalities: proteinuria <3.5g/24 hours and >0.5g/24 hours, and/or microscopic haematuria (urinary red blood cells >5/high power field (HPF) after having excluded non-renal causes and nephrotic syndrome: proteinuria ≥3.5 g/24 hours, and serum albumin <3.5g/dl.
Complete renal remission: proteinuria <0.5g/24hours, normal or near normal eGFR (within 10% of normal eGFR if previously abnormal) (28).
Active LN: all the other cases.
Arterial hypertension: the mean of three consecutive measurements of systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg in sitting position.
Proteinuria: measured by benzethonium chloride on the urine collected over 24 hours expressed as g/24 hours.
eGFR: evaluated with Cockcroft and Gault formula.

Statistical analysis
Descriptive statistics were calculated as median and interquartile ranges (IQR), since the distribution of the variables was not normal. For the same reason, the difference of continuous variables between groups was tested with non-parametric Mann-Whitney test for independent samples. Chi-square test was used to test correlations of qualitative or dichotomised variables between groups of patients.
Chronic damage accrual was assessed as the first change in SDI score. We performed univariate and multivariate Cox proportional hazard analysis to identify the predictors of first increase in chronic damage. We tested the factors at start of induction therapy, the total amount of corticosteroids administered and the proportion of follow-up in complete renal remission from baseline to the first change in SDI score.
We also employed a linear regression model to establish the predictors of all chronic organ damages, considering the total SDI scores of each patient adjusted for the duration of the follow-up. All the variables reported in Table I have been tested as predictors of SDI score increase and of death. In the multivariate analysis, we tested all the variables with $p \leq 0.05$ at univariate analysis and those having a potential clinical significance. Patients lost-to-follow up were censored at last observation. Kaplan-Meier estimate was used to draw survival curves, and log-rank test was used to test their difference.

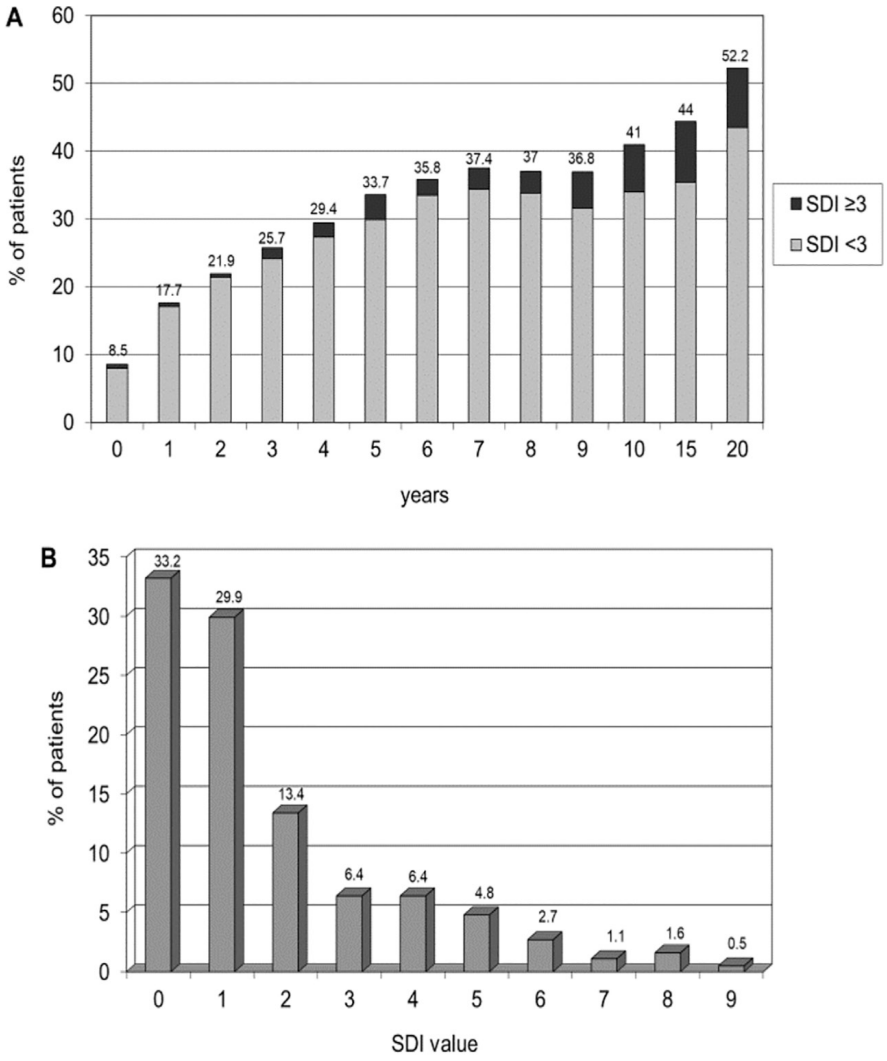

Fig. 1. A: Percentage of patients who accumulated any organ damage (SDI >0) over the years, from baseline to the 20th year after the diagnosis of lupus nephritis, and percentage of those with increased SDI score equal or greater than 3.
B: Situation at last observation regarding the percentage of patients with SDI scores from 0 to 9.

Results

One hundred and eighty-seven patients (91.4% females, median age at diagnosis of LN 28.1 years, 95.7% Caucasians) out of the 266 followed in our Renal Unit were included in this retrospective study of a prospective followed cohort (Table I). Six patients were excluded for CKD at diagnosis, 21 for incomplete data and 52 because of a follow-up shorter than 5 years (see Study cohort). We compared the clinical/biochemical and therapeutic characteristics of the 52 patients excluded for the short follow-up and of those included in the study (Supplementary Table S1). There were no significant differences between the two groups. At inclusion in the study 16 patients (8.5%) had SDI>0. The duration of SLE before the diagnosis of LN was 0.3 years (IQR 0–4.2). At renal biopsy 3 patients had class II, 42 had class III (14 class III+V), 100 had class IV (9 class IV+V) and 42 class V LN. The median activity index was 6 (IQR 3-9), and chronicity index was 2 (IQR 1–3). At diagnosis of LN 69% of patients had

normal renal function, 31% had acute renal dysfunction, and 49.7% had arterial hypertension. The type and the association of anti-hypertensive therapy is reported in Table I. In addition, 41 normotensive patients were treated with ACEi/ARB (Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers) to reduce proteinuria. Induction and maintenance therapy after renal biopsy are reported in Table I. We reported the induction and the maintenance therapies employed during the different decades of the study (Suppl. Table S2). From the start of induction therapy to the first increase of SDI score, the cumulative median dosage of prednisone was 7.1mg/day (IQR 4.7–10.8) and the percent of follow-up spent in complete renal remission was a median of 47% (IQR 13.8–75.5).

At last observation, after a median follow-up of 18.6 years (IQR 11.2–25), sixty-two percent of patients accrued irreversible organ damage (a total of 285 episodes of damage accrual in 116 patients). To evaluate a possible reduction in SDI progression across different decades, we divided our time span in three periods: 1970–1985, 1986–2001, 2002–2019. For any patient we calculated the annual rate of SDI score (obtained dividing its total SDI score for the duration of follow-up), then we evaluated the mean annual rate of SDI in the three different periods. The mean annual rate of SDI was 0.14±0.17 in the first period, it reduced to 0.09±0.21 in the second period and to 0.07±0.1 in the third period. The difference was significant: p=0.0032.

Figure 1A shows the percentage of patients who accumulated any organ damage (SDI>0) over the years, from baseline to the 20th year after the diagnosis of LN, and the percentage of those with increased SDI score equal or greater than 3. Figure 1B shows the situation at last observation regarding the percentage of patients with SDI scores from 0 to 9 (the maximum observed in our cohort). Renal domain had the highest rate of SDI increase (22.5%) with eGFR<50ml/min/1.73m^2 in 18 patients and end stage renal disease in 24 patients. The other domains frequently involved were ocular (18.2%), cardiovascular and neuropsychiatric (13.4% each) and malignancy (12.8%) (Fig. 2). At the last observation 26 patients (13.9%) had died.

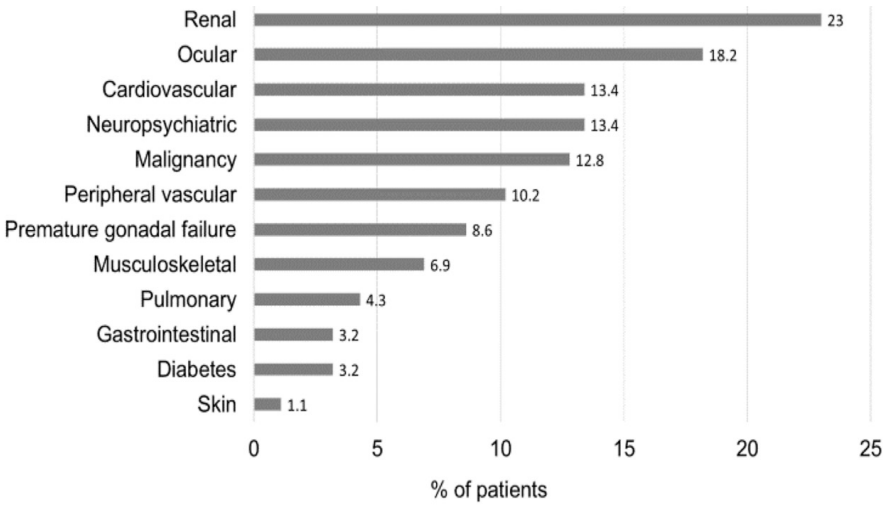

Fig. 2. Distribution of chronic damage in the different organ domains.

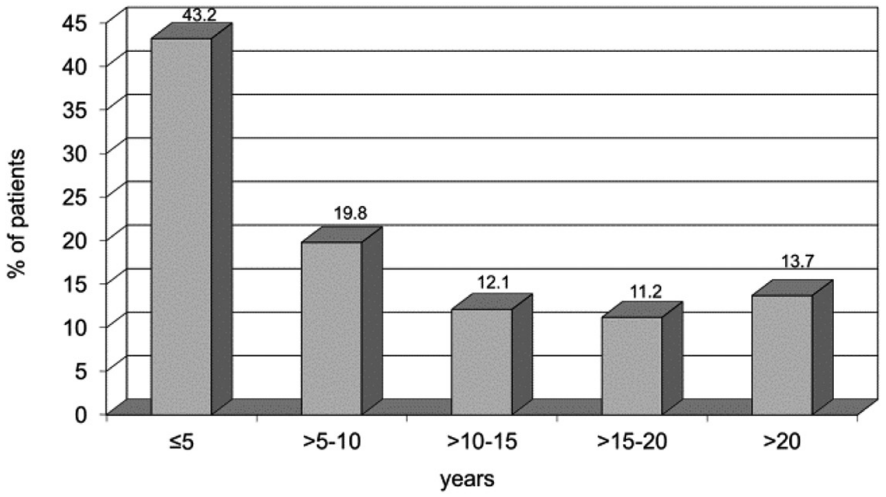

Fig. 3. Percentage of patients who developed the first SDI score increase from one to 20 years after lupus nephritis diagnosis.

Rate and predictors of first SDI score increase

One hundred and sixteen patients (62% of the cohort) developed a first SDI increase during a follow-up of more than 18 years. A comparison between the clinical characteristics of patients who did not and of those who accrued the first damage is reported in Table I.

The percentage of patients who developed the first SDI score increase from one to 20 years after LN diagnosis is shown in Figure 3. More than 40% of all first SDI score increases were recorded within the first 5 years after LN diagnosis and another 20% between 5 and 10 years. The first SDI score increase free survival at 5, 10, 15 and 20 years was 73.3%, 59.8%, 49.9% and 38% (Suppl. Fig. S1).

At univariate Cox regression analysis, among the demographic characteristics, the age at diagnosis of SLE (HR 1.028, CI:1.013–1.043, p=0.0003) and of LN (HR 1.025, CI:1.009–1.041, p=0.001) predicted the first SDI increase. Among the baseline biochemical features, serum creatinine >1mg/dl (HR 1.693, CI:1.176–2.437, p=0.005), eGFR <60ml/min/1.73m^2 (HR 1.747, CI:1.179–2.589 p=0.005), serum albumin (HR 1.621, CI:1.116–2.354, p=0.012), presentation with acute renal dysfunction (HR 1.565, CI:1.074–2.279, p=0.019) and arterial hyper-

tension (HR 1.937, CI:1.328–2.824, p=0.0006) were significantly associated with occurrence of the first damage. None of the immunosuppressive drugs administered as induction and as maintenance therapy was correlated to the first SDI score increase. Instead, cumulative prednisone dosage was strongly correlated to development of new chronic damage. In particular an average prednisone dosage >5mg/day increased the risk of the occurrence of first new damage of 3.933 times (CI:2.362–6.548, p<0.0001). The achievement of complete renal remission (HR 0.987, CI:0.981–0.993, p<0.0001), in particular for at least 40% of the follow-up (HR 0.560, CI:0.388–0.810, p=0.002) and the use of hydroxychloroquine (HR 0.675, CI:0.464–0.983, p=0.040) reduced the risk of the occurrence of the first damage.

At multivariate analysis, presentation with acute renal dysfunction (HR 1.587, CI:1.082–2.327, p=0.018) (Fig. 4A), arterial hypertension (HR 1.669, CI:1.126–2.475, p=0.011) (Fig. 4B), average prednisone dose >5mg/day (HR 3.378, CI:1.984–5.751, p<0.0001) (Fig. 4C) and achievement of complete renal remission (HR 0.993, CI:0.987–0.999, p=0.039) were the independent predictors of damage accrual (Table II).

Predictors of all the chronic organ damage

At last observation, 285 increases of SDI score occurred in our cohort. For each patient we considered all the damages accrued adjusted for the duration of the follow-up. These data were employed in a linear regression model to find the predictors of total chronic organ damage (Suppl. Table S3). At multivariate analysis, low eGFR (p=0.025), arterial hypertension (p=0.030), chronicity index at renal biopsy (p=0.008), average prednisone dose during the follow-up (p<0.001) and percentage of follow-up in complete remission (p=0.028) were the independent predictors of damage accrual.

Causes and predictors of mortality

The 26 deaths occurred at a median age of 60.3 years (IQR 46.8–66.5) and all occurred after the tenth year of follow-

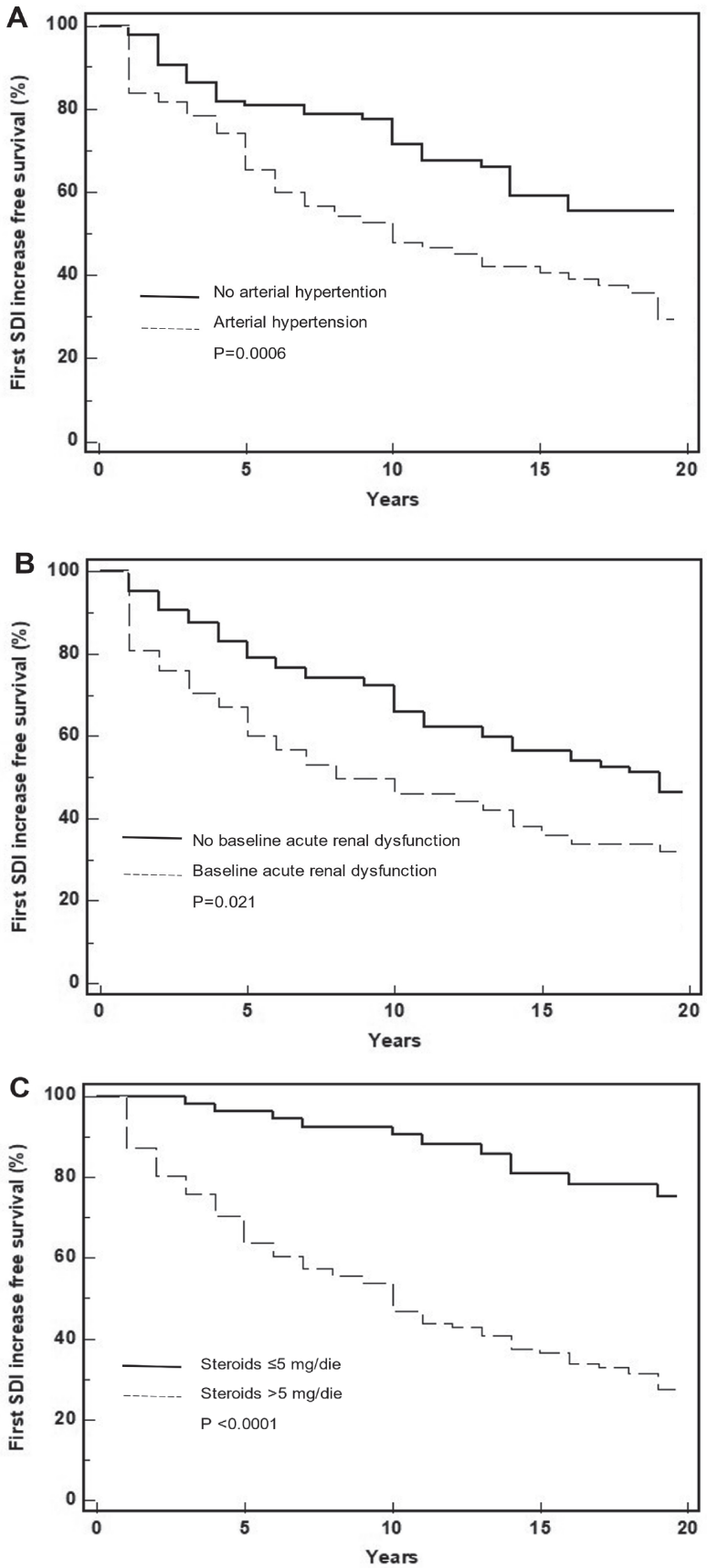

Fig. 4. First SDI score increase free survival. **A**) in patients with and without acute renal dysfunction at baseline. **B**) in patients with and without arterial hypertension. **C**) in patients with average prednisone dose > or ≤5 mg/day.

Table II. Predictors of the first SDI increase and of death at univariate and at multivariate Cox regression analysis among the features at diagnosis and of outcome of lupus nephritis.

	Univariate analysis			Multivariate analysis		
	HR	CI	*p*-value	HR	CI	*p*-value
Predictors of first SDI increase						
Age at SLE, years	1.028[a]	1.013-1.043	0.0003			
Age at LN, years	1.025[a]	1.009-1.041	0.001			
Serum creatinine >1mg/dl	1.693	1.176-2.437	0.005			
eGFR<50ml/min/1.73mq	1.747	1.179-2.589	0.005			
Arterial hypertension	1.937	1.328-2.824	0.0006	1.669	1.126-2.475	0.011
Acute renal dysfunction [b]	1.565	1.074-2.279	0.019	1.587	1.082-2.327	0.018
Serum albumin <3mg/dl	1.621	1.116-2.354	0.012			
% of follow-up in complete renal remission	0.987	0.981-0.993	<0.0001	0.993	0.987-0.999	0.039
≥40% of follow-up in complete renal remission	0.560	0.388-0.810	0.002			
Cumulative average PDN mg/day	1.203	1.162-1.246	<0.0001			
Average PDN dose >5mg/day	3.933	2.362-6.548	<0.0001	3.378	1.984-5.751	<0.0001
Hydroxychloroquine	0.675	0.464-0.983	0.040			
Predictors of death						
Age at SLE, years	1.059*	1.026-1.093	0.0004			
Age at LN, years	1.070*	1.037-1.105	0.0001	1.063	1.027-1.099	0.0004
Arterial hypertension	3.351	1.339-8.388	0.005	3.096	1.211-7.912	0.019
Baseline low C4	1.028	1.007-1.049	0.035			
No maintenance therapy with IS	3.435	1.014-11.636	0.024	4.168	1.212-14.336	0.024
Hydroxychloroquine	0.310	0.115-0.832	0.020			
SDI score increase *vs*. no increase	9.164	1.231-68.202	0.031			
% of follow-up in complete renal remission	0.919	0.874-0.966	0.0009			

HR: hazard ratio; CI: confidential interval; SLE: systemic lupus erythematosus; LN: lupus nephritis; eGFR: estimated glomerular filtration rate; SDI: SLICC damage index; IS: immunosuppressors; PDN: prednisone.
[a] for any year of increase
[b] nephritic syndrome + rapidly progressive renal insufficiency *vs*. urinary abnormalities + nephrotic syndrome.
Unless differently specified, the data are reported as median and interquartile ranges.

up (in median of 21.3–years, IQR 14.8–26.9 after LN diagnosis). At time of death, the median SDI score was 4 (IQR 2-6) in the 26 deceased patients in comparison to SDI 1 (IQR 0-2) at last observation in those alive (p=0.0001). The causes of deaths were infections in 2 patients (7.7%), cardiovascular and cerebrovascular accidents in 15 (57.7%), neoplasia in 6 (23.1%), and unknown in 3 patients (11.5%) (Table III).

At univariate analysis, among the baseline characteristics, age at diagnosis of SLE (HR 1.059, CI:1.026–1.093, p=0.0004) and of LN (HR 1.070, CI:1.037–1.105, p=0.0001), arterial hypertension (HR 3.351, CI:.339–8.388, p=0.005), low C4 (HR 1.028, CI:1.007–1.049, p=0.035), no maintenance therapy with immunosuppressive drugs (HR 3.435, CI:1.014–11.636, p=0.024), increase in damage *versus* no increase (HR 9.164, CI:1.231–68.202, p=0.031) predicted new damage. Instead, the use of hydroxychloroquine (HR 0.310, CI:0.115–0.832, p=0.020) and achievement of complete renal remission (HR 0.919, CI:0.874–0.966, p=0.0009) protects from death. At multivariate analysis, age at LN diagnosis (HR 1.063, CI:1.027–1.099, p=0.0004), arterial hypertension (HR 3.096, CI:1.211–7.912, p=0.019) and no maintenance therapy with immunosuppressive drugs (HR 4.168, CI:1.212–14.336, p=0.024) were the independent predictors of death (Table II).

Discussion

In this study, we reported the rate and the predictors of first increase in SDI score in a large cohort of biopsy proven LN patients followed for more than 18 years in a single tertiary Italian Nephrological centre. We found that: 62% of patients accrued damage and that the first damage free survival reduced from 73.3% at five years to 38% at 20 years. Around 40% of the first increases in SDI score occurred during the first five years after LN diagnosis, then the rate of developed of first damage decreased. Considering the first and the subsequent damages, at last observation 40 patients (23.5%) had extensive damage with SDI higher or equal than 3. However, our results seem to show a progressive reduction in damage accrual during the last decades. In particular, the mean annual rate of SDI progressively reduced from the period 1970–1985, to that 1986–2001 and to that 2002–2019. This improvement could be attributed to the progressively less severe clinical presentation of LN reported in our previous study (27).

As expected, the renal domain accumulated the higher rate of damage in our cohort. In around one quarter of patients, SDI increase was due to CKD development, with end stage renal disease in more than 50% of them. In addition to renal domain, others life-threatening complications, such as those in cardiovascular and neurological domains and malignancies, were the most frequent causes of SDI increase in LN patients.

Table III. Comparison between dead and alive patients at the end of follow-up.

	Alive patients 161 patients	Dead patients 26 patients	*p*-value
Baseline characteristics			
Female, n (%)	148 (91.9)	23 (88.5)	0.481
Caucasian / other ethnicities n (%)	153 (95) / 8 (5)	26 (100) / 0	0.783
Duration of SLE before LN diagnosis, years	0.4 (0-4.7)	0.1 (0-3.4)	0.901
Age at SLE diagnosis, years	24.3 (19.2-32.9)	28.5 (22.6-41.9)	**0.024**
Age at LN diagnosis, years	27.7 (21.2-37)	32.3 (26.6-45.9)	**0.023**
Diagnosis before 2000, n (%)	96 (59.6)	23 (88.5)	**0.004**
Serum creatinine, mg/dl	0.9 (0.7-1.3)	1.1 (0.8-1.8)	**0.031**
Serum creatinine >1 mg/dl, n (%)	61 (37.9)	15 (57.7)	0.056
eGFR <60ml/min/1.73mq, n (%)	47 (29.2)	12 (46.1)	0.087
Proteinuria g/24h	3.6 (1.8-5.3)	3 (1.6-5.2)	0.628
Arterial hypertension, n (%)	73 (45.3)	20 (76.9)	**0.003**
Acute renal dysfunction, n (%)	46 (28.6)	12 (46.1)	0.072
Serum albumin, mg/dl	2.9 (2.3-3.5)	2.7 (2.3-3.3)	0.310
C3, mg/dl	58 (48-79)	56.5 (50-74.5)	0.469
C4, mg/dl	11 (6-15)	10 (5-20)	**0.011**
Antiphospholipid antibodies, n (%)	31 (19.2)	8 (30.8)	0.185
Class II+V, n (%), Class III+IV, n (%)	38 (23.6), 123 (76.4)	7 (26.9), 19 (73.1)	0.712
Activity index	6 (3-9)	6 (3.5-9)	0.967
Chronicity index >1, n (%)	73 (45.3)	12 (46.2)	0.943
SDI, mean	0.1 (±0.4)	0.1 (÷0.3)	0.917
SDI >0, n (%)	14 (8.2)	2 (12.5)	0.548
SLEDAI	15 (10-19)	15 (11.3-19)	0.860
Methylprednisolone pulses, n (%)	129 (80.1)	14 (53.8)	**0.0007**
Induction therapy with IS, n (%)	127 (78.8)	18 (69.2)	0.27
CYC, n (%)	86 (53.4)	10 (38.5)	0.163
Hydroxychloroquine, n (%)	96 (59.6)	5 (19.2)	**0.0001**
Characteristics from lupus nephritis diagnosis to the end of follow-up			
Maintenance therapy with IS, n (%)	86 (53.4)	3 (11.5)	**<0.0001**
% of follow-up spent in complete renal remission	46.3 (22.9-78.6)	29.7 (0-53.1)	0.081
Patients with SDI increase >0, n (%)	91 (56.5)	25 (96.2)	**0.0001**
SDI at the end of follow-up	1 (0-2)	4 (2-6)	**<0.0001**
Arterial hypertension at the end of follow-up, n (%)	77 (47.8)	20 (76.9)	**0.006**

SLE: systemic lupus erythematosus; LN: lupus nephritis; eGFR: estimated glomerular filtration rate; SDI: SLICC Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; IS: immunosuppressors; CYC: cyclophosphamide.
Unless differently specified, the data are reported as median and interquartile ranges.

Since high SDI scores in SLE patients have been shown to be associated with increased mortality (3, 5, 29, 30), it is important to identify the factors associated with the development of organ damage over time. In our cohort, in addition to some well recognised predictors of organ damage, such as older age and arterial hypertension (4, 14, 16, 31, 32), we found that acute renal dysfunction at LN diagnosis was strongly associated with SDI progression. This clinical situation suggests the need for a prompt institution of aggressive treatment to prevent not only the transformation of acute into chronic renal dysfunction, but also SDI increase. Ultimately, a timely diagnosis of LN and renal biopsy are mandatory to prevent SDI increase. In keeping with previous studies in SLE (3, 10, 19, 33, 34), cumulative corticosteroid dose was independently associated with development of damage in our cohort. A prednisone dose >5mg/day independently predicted the first damage development. Accordingly, corticosteroids should be reduced to the lowest possible dose during the quiescent phases of the disease to reduce SDI progression. Some new drugs, such as biological drugs or rapamycin, may be helpful in reducing the cumulative steroid dosage as suggested by some recent studies (7, 35).

On the other hand, the treatment with hydroxychloroquine protected from the increase of damage as demonstrated by Bruce *et al*. (3) and by Petri *et al*. (19). In contrast with other studies, SLEDAI (3, 10, 31, 32, 35, 36) score and SDI >0 at baseline (3, 4, 31) were not associated with increased damage, however, only a minority of our patients had SDI >0 at the beginning of the study.

The importance of renal involvement in SLE patients as a predictor of damage accrual was demonstrated in some (19, 31-33, 37, 38) but not in all SLE studies (3, 4, 34, 39). In the LUMINA multi-ethnic SLE cohort, LN emerged as the most important predictor of damage accrual (38). In the study of Petri *et al*. (19), the mean rate of increase in the SDI score was 0.13 per year in the whole SLE population, but this value increased to 0.17 per year in patients with proteinuria. Active renal disease at baseline (31) and during the follow-up (3) predicted SDI progression in cohorts of SLE that included patients with any organ involvement. In a large multinational prospective cohort of LN patients followed for two years, Kandane-Rathnayake *et al*. reported that active LN predicted renal but not non renal damage (21). However, only 33% of patients had biopsy proven LN, and LN activity was based on SLEDAI urinary parameters that did not include renal function. In a multinational cohort of 502 patients, followed for 3.6 years, Reátegui-Sokolova *et al*. identified high SLEDAI score in renal domains as predictor of renal damage (22). However, similarly to the previously mentioned study (21), the diagnosis of LN was based only on clinical features that did not include renal function. Moreover, more than half of the patients did not receive a renal biopsy (22). Renal dysfunction at diagnosis is considered the most important predictor of renal survival in any renal disease (40). In our cohort all patients had biopsy proven LN and activity and remission of LN during the follow-up were evaluated based on the EULAR/EDTA recommendations, that includes both renal function and proteinuria (28, 41).

We found that the achievement of prolonged renal remission and a remission lasting 40% of the follow-up protects from damage accrual, confirming the

results of studies in SLE patients with any organ involvement (9, 33, 34, 42). Although a number of studies in LN demonstrated that the achievement of renal remission predicts good long-term renal outcome (43, 44), no data are available about the beneficial effects of remission in reducing damage accrual. The achievement of complete renal remission emerged as an independent predictor of SDI progression at multivariate analysis, together with prednisone dose, acute renal dysfunction at baseline and arterial hypertension.

There is an almost unanimous consensus that the presence of arterial hypertension is associated with an increase in chronic damage (3, 13, 33, 37), not only in the SLE but in the general population too (45, 46). Although, in clinical trials, intensive blood pressure control did not slow the progression of CKD, intensive control reduced the risk for adverse cardiovascular outcomes and mortality (47). In our cohort arterial hypertension was confirmed as an independent predictor not only of SDI increase, but also of mortality together with older age. Of note, in all our patients, arterial hypertension present at diagnosis persisted throughout the whole follow-up.

Two therapeutic approaches seem to protect from mortality: the use of hydroxychloroquine and that of an immunosuppressor as maintenance after induction therapy. Among the broad spectrum of beneficial effects of hydroxychloroquine in SLE patients, a reduction of mortality was also reported (48, 49), and our data are in keeping. The importance of a maintenance therapy with an immunosuppressor to improve LN renal survival was first reported by Mok *et al*. (50) and recently confirmed by our multicentre study (27).

The limitations of this study include the retrospective design of the study, the limited sample size (considering recent randomised controlled trials of lupus nephritis and registries), and Caucasian ethnicity in most of our patients, which precludes the possibility to extend these results to other ethnicities. In addition, we did not evaluate some time-dependent factors, such as renal and extra renal flares.

Despite the retrospective nature of the study, this is a LN cohort with a very long follow-up. This can help in defining the long-term renal outcome and the impact of SDI on renal prognosis. We found that the clinical presentation of LN has an important role in predicting SDI increase. This suggests the need for timely renal biopsy and rapid institution of therapy to normalise renal function and to achieve a long-lasting remission; both conditions are necessary to protect from chronic damage. The use of the lowest possible dose of corticosteroids during the quiescent phases of the disease and strict control of arterial hypertension should be the ultimate goals to prevent SDI progression in LN.

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