Title

Predictors of Remission and Low Disease Activity State in Systemic Lupus Erythematosus: Data from a multi-ethnic, multinational Latin-American Lupus Cohort

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ON BEHALF OF GLADEL

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ACKNOWLEDGMENTS

We are grateful to Daniel Villalba and Leonardo Grasso for providing expert assistance with the ARTHROS (version 6.0) software. Preliminary results were presented at the 2017 12th International Congress on SLE.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting or critically revising this manuscript for important intellectual content, and all authors approved the final version to be published. Drs. Manuel F. Ugarte-Gil, Daniel Wojdyla, Graciela S. Alarcón and Bernardo A. Pons-Estel have full access to all the study's data and take responsibility for their integrity and the accuracy of the analyses performed.

FUNDING INFORMATION

The GLADEL cohort received no specific funding from agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

Predictors of Remission and Low Disease Activity State in Systemic Lupus Erythematosus: Data from a multi-ethnic, multinational Latin American Lupus Cohort

Objective: To determine the predictors of remission and low disease activity state (LDAS) in systemic lupus erythematosus (SLE).

Materials and methods: Three disease activity states were defined: Remission=SLEDAI=0 and prednisone≤5mg/d and/or immunosuppressants (maintenance dose); LDAS=SLEDAI≤4, prednisone≤7.5mg/d and/or immunosuppressants (maintenance dose); and non-optimally controlled state=SLEDAI>4 and/or prednisone>7.5mg/d and/or immunosuppressants (induction dose). Antimalarials were allowed in all groups. Patients with at least two SLEDAI reported and not optimally controlled at cohort entry were included in these analyses. Outcomes were remission and LDAS. Multivariable Cox regression models (stepwise selection procedure) were performed for remission and for LDAS.

Results: Of 1480 patients, 902 were non-optimally controlled at cohort entry; of them, 196 patients achieved remission (21.7%) and 314 achieved LDAS (34.8%). Variables predictive of a higher probability of remission were the absence of mucocutaneous manifestations [HR=1.571 (95%CI 1.064-2.320)], of renal involvement [HR=1.487 (95%CI 1.067-2.073)], and of hematologic involvement [HR=1.354 (95%CI 1.005-1.825)]; the use of immunosuppressive drugs before the baseline visit [HR=1.468 (95%CI 1.025-2.105)] and a lower SLEDAI at cohort entry [HR=1.028 (95%CI 1.006–1.051) per 1 unit decrease]. Older age at cohort entry, per five years increase [HR=1.050 (95%CI 1.004-1.098)]; absence of mucocutaneous manifestations [HR=1.401 (95%CI 1.016-1.930)], and renal involvement [HR=1.344 (95%CI 1.049-1.721)] as well as a lower SLEDAI at cohort entry [HR=1.025 (95%CI 1.009–1.042)] were predictive of LDAS.

Conclusions: The absence of mucocutaneous, renal and hematologic involvement, the use of immunosuppressive drugs and a lower disease activity early in the course of the disease were predictive of remission; older age was predictive of LDAS.

Keywords: Systemic lupus erythematosus, remission, low disease activity state, risk factors.

Introduction

Treat to Target strategy (T2T) has been proposed in systemic lupus erythematosus (SLE) (1, 2), but the proper target remains to be elucidated. Remission, in particular remission off-therapy is uncommon; for example, in the GLADEL (*Grupo Latino Americano De Estudio de Lupus*) cohort, only 3.7% of the patients achieved remission at least once in the interval between two visits during their follow-up; per protocol, visits were performed every six months(3). In the Toronto Cohort 1.7% of the patients achieved remission for at least five years and 10.2% for at least one year (4) and in the LCTC registry (Lupus Clinical Trials Consortium) 5.4% of the patients achieved remission for at least one year (5). In predominantly Caucasian cohorts, the incidence of remission is higher; for example in an Italian study, 7.1% of the patients achieved remission for at least five years (6), whereas 12.8% did so in a cohort from the Netherlands (7).

An alternative outcome, remission on-therapy, is still rare; 16.5% of patients from the GLADEL cohort achieved it at least once in the intervals between two visits during the follow-up (3), 18.9% of the Toronto cohort (4) and 7.6% of LCTC cohort achieved this outcome for at least one year (5).

A less stringent target (low disease activity state, [LDAS]), has been found in 14.2% of patients from the GLADEL cohort at least once in the intervals between visits during their follow-up (3) and in 14.9% of those from LCTC (5); additionally, to those on remission, 85% of the patients in the Asia-Pacific Lupus Collaboration (APLC) achieved LDAS at least once (8) whereas 76.0% of the patients in the Netherlands cohort did so (7).

Given that achieving either remission or LDAS seems to be protective in term of new damage (3, 6-11), mortality (10) and the occurrence of flares (10), achieving these states seems quite important in the management of patients with SLE. However, how long these states should last and how frequently they need to be assessed remains to be elucidated. The DORIS group (Definitions Of Remission In SLE) has suggested that duration should be examined at six and 12 months from disease onset and then at two and five years (12).

The aim of this study was to evaluate the factors associated with achieving remission or LDAS in SLE patients not optimally controlled from the GLADEL cohort.

Material and Methods

Patients.

The GLADEL cohort is an observational inception cohort study started in 1997 in 34 centers from nine Latin American countries. A common protocol, consensus definitions, and outcome measures were established. The general characteristics and composition of the GLADEL cohort patients have been described in detail elsewhere (13, 14). However, given that this cohort was started in 1997, time at which a signed informed consent for observational research studies was not required at all participating centers involved in this cohort, we do not have such documentation for each cohort patient; likewise, in 1997 most participating GLADEL centers did not have formal ethics committees. Nevertheless, the study was performed according with the declaration of Helsinki for the conduct of research in humans and following local institutional review boards regulations.

For these analyses, three disease activity states were defined: Remission: SLEDAI = 0 and a prednisone dose ≤5mg/day and/or immunosuppressive drugs (IS) (maintenance dose); LDAS = not on remission, and, SLEDAI ≤4, a prednisone dose ≤7.5mg/day and/or IS (maintenance dose); and non-optimally controlled state = SLEDAI >4 and/or prednisone dose >7.5mg/day and/or IS (induction dose) (3). Antimalarials were allowed in all groups. These states were evaluated using the interval between two SLEDAIs or the last SLEDAI and the end of the follow-up. Only patients who were non-optimally controlled at the time of the first SLEDAI and with at least one subsequent SLEDAI measurement were included in the analyses.

Variables.

Demographic characteristics including gender, age at diagnosis, ethnicity, socioeconomic status (SES) (15), level of education, urban/rural residence and health insurance were evaluated.

Disease characteristics such as disease duration at cohort entry and organ or systems affected at or before cohort entry were included. Clinical manifestations were grouped into eleven domains: general manifestations: fever, weight loss and lymphadenopathies; muscular manifestations: myalgia and myositis; articular manifestations: arthralgia, arthritis, Jaccoud's arthropathy, overall musculoskeletal related to SLE, and osteonecrosis; cutaneous manifestations: alopecia, photosensitivity, malar rash, discoid rash, mucosal ulcers, panniculitis, livedo reticularis, subacute cutaneous lupus, bullous lupus, Raynaud's phenomenon, and overall cutaneous related to SLE; ocular manifestations: xerophthalmia, keratoconjuctivitis sicca, scleritis, episcleritis, uveitis, retinopathy, cytoid bodies, amaurosis, and overall ophthalmic related to SLE and cataracts; respiratory manifestations: lung serositis, interstitial lung disease, alveolar hemorrhage, pulmonary thromboembolism, pulmonary hypertension, shrinking lung, lung infarction and overall respiratory related to SLE; cardiovascular manifestations: pericarditis, myocarditis, endocarditis, rhythm disorders, hypertension, ischemic heart disease, coronary artery disease, atherosclerosis, thrombosis, peripheral artery disease and overall cardiovascular related to SLE; renal manifestations: proteinuria, cellular casts, glomerulonephritis, tubular interstitial alterations, renovascular disease, renal failure (acute or chronic) and overall renal related to SLE;

neuropsychiatric manifestations: psychosis, seizures, neurologic syncope, vertigo, mood disorders, cognitive dysfunction, acute confusional state, dementia, motor/sensitive disorders, movement disorders, myelopathy, mononeuritis multiplex, polyneuropathy, cranial neuropathy, autonomic neuropathy, lupus headache and overall neurologic related to SLE; digestive manifestations: peritoneal serositis, xerostomy and overall digestive related to SLE; and hematologic manifestations: autoimmune hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia and overall hematologic related to SLE.

Disease activity was ascertained using the SLEDAI (16), and it was assessed, per protocol, twice a year.

Disease damage was ascertained using the SLICC/ACR damage index (SDI) (17) and was measured, per protocol, once a year.

Glucocorticoid use was recorded as the highest dose at or before cohort entry, and it was categorized as low dose: prednisone ≤7.5 mg/d, medium dose: >7.5-≤15 mg/d, high dose: >15-<60 mg/d, very high dose: ≥60 mg/d. Parenteral glucocorticoids were not included. Antimalarial and IS were recorded as ever used or not used. Treatment was recorded at or before cohort entry.

Statistical Analyses

Patients with and without remission and LDAS during follow-up were compared using frequencies and percentages for categorical variables and median and 25th – 75th percentiles for continuous variables. Cox regression models were used to derive p-values comparing the incidence of these outcomes for each baseline characteristic. For each outcome, a multivariable Cox regression model was derived using a backward selection method with α-level to stay in the model set at 0.05. Antimalarials use was included as a time-dependent covariate. All variables included in the descriptive analysis were considered as candidates for inclusion in the multivariable model except education and immunological involvement which were excluded due to missing values. Two alternative models were performed, one excluding serology and the second excluding those manifestations which are probably not related with disease activity, including the variables grouped per organ/system or individually, for those manifestations present in at least 20% of the patients. Continuous variables were tested for linearity and linear splines were used in case of non-linearity. The proportional hazard assumption was tested using the Schoenfeld residuals. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc, Cary, NC).

Results

Nine hundred and two patients were non-optimally controlled at cohort entry (Supplementary Figure 1), 809 (89.7%) were female, with a median age at diagnosis of 26 years (25th–75th percentiles: 20-36), the median length of follow-up was 56.3 (35.6-7.16) months. Characteristics of these patients are depicted in Table 1.

One hundred and ninety-six patients achieved remission (21.7%); of them 97 were followed for at least three years after achieving remission and 47 (48.5%) of them achieved prolonged remission; 314 achieved LDAS (34.8%); of them, 164 were followed for at least three years after achieving LDAS; 92 (56.1%) out of 164 were on prolonged LDAS. The distribution of characteristics among those who achieved or not remission is depicted in Table 2 and for those who achieved or not LDAS in Table 3. Briefly, those who achieved remission belonged more frequently to a higher SES and were more educated; they also had a lower frequency of mucocutaneous and renal involvement and a lower SLEDAI at baseline. Patients who achieved LDAS were older at diagnosis and at baseline, had a higher SES, were more educated, had a lower frequency of general, mucocutaneous, and renal involvement, had used higher doses of prednisone, had a lower SLEDAI at baseline.

In multivariable analyses, the absence of mucocutaneous manifestations [HR=1.571 (95%CI 1.064-2.320)], of renal involvement [HR=1.487 (95%CI 1.067-2.073)], and of hematologic involvement [HR=1.354 (95%CI 1.005-1.825)]; the use of immunosuppressive drugs before baseline [HR=1.468 (95%CI 1.025-2.105)] and a lower SLEDAI at cohort entry [HR=1.028 (95%CI 1.006-1.051) per 1 unit decrease] were predictors of patients' achieving remission. Older age at cohort entry, per five years increase [HR=1.050 (95%CI 1.004-1.098)]; absence of mucocutaneous manifestations [HR=1.401 (95%CI 1.016-1.930)], and renal involvement [HR=1.344 (95%CI 1.049-1.721)] as well as a lower SLEDAI at cohort entry [HR=1.025 (95%CI 1.009– 1.042)] were also predictive of patient's achieving LDAS. The final multivariable models are depicted in Tables 4 and 5. Kaplan-Meier curves representing these multivariable analyses are shown in Figure 1 (A-D) and Supplementary Figure 2 (A-D).

Using the alternative models, when we excluded serology, the results were very similar than those with serology and when we included independently those manifestations presented in at least 20% of our patients, the predictors of remission were the absence of fever, photosensitivity, cellular casts and hematologic involvement as well as the use of immunosuppressive drugs and a lower SLEDAI (data not shown).

Discussion

Utilizing the longitudinal data from GLADEL, a multi-ethnic, multinational inception cohort, we have evaluated the predictors of achieving remission or LDAS/remission. Of importance, the absence of mucocutaneous manifestations and of renal involvement and lower disease activity early in the course of SLE were associated with a higher probability of patients achieving remission and LDAS while a higher SES was associated with an increased probability of remission and a medium prednisone dose was associated with a higher probability of LDAS.

Although there is no uniformity about the factors associated with achieving remission and LDAS, some variables have been found in more than one study. For example, like in the current study, older age has been reported to be associated with remission or LDAS in studies from the UK (18), China (19) and the Netherlands (7). Ethnicity was found to be associated with remission in the Toronto Cohort; those who achieved prolonged remission (more than five years) were more frequently Caucasians (9); this was also the case in the UK cohort (18). Caucasian ethnicity has also been associated with LDAS as reported in the Netherlands cohort where Caucasians achieved more frequently LDAS for at least 50% of the follow-up time (7). In turn, in the Hopkins Cohort, African Americans had a lower probability of achieving remission (20). We found no such association in our cohort. However, the association between ethnicity and a lower probability of achieving remission or LDAS may relate to factors associated with ethnicity (health disparities, lower SES) and not necessarily due to ethnicity per se.

Similar to our findings, the absence of mucocutaneous involvement has been found to be associated with a higher probability of remission in some studies but not in all. A higher probability was found in the Toronto cohort (9) and the aforementioned UK study (18) but not in the Padova (6), the Netherlands (7), Hopkins (20) and a Chinese (19) lupus cohort; absence of mucocutaneous involvement has also been associated with a higher probability of achieving LDAS in the APLC cohort (21). On the other hand, absence of renal involvement has been associated with a higher probability of achieving remission in several cohorts [Padova (6), UK (18), the Netherlands (7) and Chinese (19)] but not in the Toronto (9) or the Hopkins (20) cohorts. Absence of renal involvement has also been associated with a higher probability of achieving LDAS in the APLC cohort (21) but not in the Netherlands cohort (7). Similarly, absence of hematologic involvement has been reported in the Hopkins (20), Padova (6) and Chinese (19) cohorts. Absence of other disease manifestations associated with a higher probability of remission, but not in our cohort, have been central nervous system in the Toronto (9) and UK cohorts (18), pulmonary involvement in the Toronto cohort (9), cardiopulmonary in the UK (18), vasculitis in the Padova cohort (6) and immunological involvement in the Hopkins cohort (20) .

A lower SLEDAI at baseline has been associated with a higher probability of remission or LDAS/remission in our cohort; in a similar way, a lower SLEDAI at baseline and at follow up has been associated with prolonged remission in the Toronto (9) and the Netherlands (7) cohorts. In the Netherlands cohort, a lower SLEDAI-2K at baseline was found in those patients who achieved prolonged remission and in those who achieved LDAS for at least 50% of the follow-up (7). These

findings contrast with those of a Spanish cohort in which disease activity at baseline was found to be similar among those patients who achieved and those who did not achieve remission; however, this cohort only included 100 patients and its results should be viewed cautiously (22).

In terms of treatment, a lower dose of glucocorticoids at baseline or during the follow-up has been associated with prolonged remission in the Toronto (9) and the Netherlands (7) cohorts. In the Netherlands cohort, a lower use of immunosuppressive drugs was found in those patients who achieved LDAS for at least 50% of the follow-up (7). Given that we examined the use of drugs before the baseline visit, and very early in the course of the disease our results cannot be compared. Rather our data support the early but judicious use of immunosuppressive drugs use if optimal outcomes in patients with SLE are to be achieved. Of note, these drugs can also increases the risk of damage accrual (23).

Our study has some limitations. First, the relatively small number of patients who achieved remission off therapy, precluded us for examined the factors predictive of this state. Second, due to the relatively short follow-up and its variable duration, the impact of some predictors could have been underestimated. Third, as there are no uniform definitions of remission and LDAS, it is possible that had we used different definitions, our results could have been also different; however, similar definitions have been used in other studies, and they are considered reliable (4-6, 22). We must point out that manifestations which are either frequent (mucocutaneous) or which do not respond rapidly to treatment (renal), could lead to a delay on achieving remission; since our analyses were based on the examination of intervals rather than Area Under the Curve this is an important issue to consider.

Despite these limitations, our data, from a very large multi-ethnic, multinational Latin American lupus cohort, emphasize the positive impact of not having mucocutaneous, renal and hematologic involvement, of an early use of immunosuppressive drugs and of experiencing lower disease activity early in the course of the disease on a higher likelihood of achieving remission or LDAS. Additionally, our data also show the positive impact of the age on achieving LDAS. These data have practical applicability to those caring for patients with lupus.

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Table 1: Characteristics of systemic lupus erythematosus patients studied

Characteristic	Overall (N=902) [N (%) or median (25th – 75th percentiles)]
Sociodemographic Characteristics	
Gender	
Male	93 (10.3)
Female	809 (89.7)
Age at Diagnosis, years	26, 20-36
Age at First Symptom, years	25, 19-34
Age at Cohort Entry, years	27, 20-36
Ethnic Group	
Caucasian	368 (40.9)
Mestizo	378 (42.0)
African Latin American	121 (13.5)
Other	32 (3.6)
Socioeconomic Status	
High/Middle High	81 (9.0)
Middle	253 (28.1)
Middle Low/Low	565 (62.8)
Residence	
Urban	817 (91.1)
Rural	80 (8.9)
Medical Coverage	
No Coverage	135 (15.0)
Partial Coverage	227 (25.3)
Full Coverage	536 (59.7)
Education	
0-7 years	264 (30.5)
8-12 years	400 (46.2)
13 or more years	202 (23.3)
Disease Duration at Cohort Entry	
Entered at Diagnosis	545 (60.4)
Up to 6 Months	132 (14.6)
6 to 12 months	101 (11.2)
13 to 24 months	124 (13.7)
Clinical Characteristics at Cohort Entry	
General manifestations	652 (72.3)

Characteristic	Overall (N=902) [N (%) or median (25th – 75th percentiles)]
Musculoskeletal involvement	813 (90.1)
Mucocutaneous involvement	800 (88.7)
Ocular involvement	82 (9.1)
Lung involvement	40 (4.4)
Cardiovascular involvement	298 (33.0)
Renal involvement	398 (44.1)
Neurologic involvement	181 (20.1)
Hematological involvement	609 (67.5)
Immunological involvement	583 / 725 (80.4)
Treatments at Cohort Entry	
Antimalarials	279 (30.9)
Prednisone (Higher dose before baseline)	
None	427 (47.3)
Low (≤ 7.5 mg/d)	16 (1.8)
Medium (>7.5 ≤15 mg/d)	83 (9.2)
High (>15 <60 mg/d)	256 (28.4)
Very High (≥ 60 mg/d)	120 (13.3)
Immunosuppressive drugs	166 (18.4)
Disease Status at Cohort Entry	
SLEDAI at Cohort Entry	10, 6-16

SLEDAI=Systemic lupus erythematosus activity index.

Table 2: Variables Associated with Remission by Univariable Analyses

Characteristic	Remission During Follow-Up: Yes (N=196) [N (%) or median (25th – 75th percentiles)]	No (N=706) [N (%) or median (25th – 75th percentiles)]	p-value
Sociodemographic Characteristics			
Gender			0.4454
Male	18 (9.2)	75 (10.6)	
Female	178 (90.8)	631 (89.4)	
Age at Diagnosis, years	28, 21-39	26, 20-35	0.0809
Age at First Symptom, years	27, 19-37	25, 19-34	0.1806
Age at Cohort Entry, years	28, 21-40	26, 20-35	0.0644
Ethnic Group			0.9977
Caucasian	86 (43.9)	282 (40.1)	
Mestizo	80 (40.8)	298 (42.4)	
African Latin American	25 (12.8)	96 (13.7)	
Other	5 (2.6)	27 (3.8)	
Socioeconomic Status			0.0030
High/Middle High	27 (13.9)	54 (7.7)	
Middle	63 (32.5)	190 (27.0)	
Middle Low/Low	104 (53.6)	461 (65.4)	
Residence			0.0605
Urban	185 (94.9)	632 (90.0)	
Rural	10 (5.1)	70 (10.0)	
Medical Coverage			0.0676
No Coverage	17 (8.7)	118 (16.8)	
Partial Coverage	55 (28.2)	172 (24.5)	
Full Coverage	123 (63.1)	413 (58.7)	
Education			0.0095
0-7 years	50 (25.9)	214 (31.8)	
8-12 years	87 (45.1)	313 (46.5)	
13 or more years	56 (29.0)	146 (21.7)	
Disease Duration at Cohort Entry			0.1454
Entered at Diagnosis	107 (54.6)	438 (62.0)	
Up to 6 Months	24 (12.2)	108 (15.3)	
6 to 12 months	26 (13.3)	75 (10.6)	
13 to 24 months	39 (19.9)	85 (12.0)	
Clinical Characteristics at Cohort Entry			

Characteristic	Remission During Follow-Up: Yes (N=196) [N (%) or median (25th – 75th percentiles)]	Remission During Follow-Up: No (N=706) [N (%) or median (25th – 75th percentiles)]	p-value
General manifestations	135 (68.9)	517 (73.2)	0.0742
Musculoskeletal involvement	183 (93.4)	630 (89.2)	0.5158
Mucocutaneous involvement	165 (84.2)	635 (89.9)	0.0490
Ocular involvement	21 (10.7)	61 (8.6)	0.6735
Lung involvement	7 (3.6)	33 (4.7)	0.3088
Cardiovascular involvement	60 (30.6)	238 (33.7)	0.5569
Renal involvement	68 (34.7)	330 (46.7)	0.0085
Neurologic involvement	35 (17.9)	146 (20.7)	0.4796
Hematological involvement	122 (62.2)	487 (69.0)	0.0655
Immunological involvement	123 / 157 (78.3)	460 / 568 (81.0)	0.3216
Treatments at Cohort Entry			
Antimalarials	69 (35.2)	210 (29.7)	0.3478
Prednisone (Higher dose before baseline)			0.1604
None	86 (43.9)	341 (48.3)	
Low (≤ 7.5 mg/d)	5 (2.6)	11 (1.6)	
Medium (>7.5 ≤15 mg/d)	21 (10.7)	62 (8.8)	
High (>15 <60 mg/d)	50 (25.5)	206 (29.2)	
Very High (≥ 60 mg/d)	34 (17.3)	86 (12.2)	
Immunosuppressive drugs	46 (23.5)	120 (17.0)	0.1139
Disease Status at Cohort Entry			
SLEDAI at Cohort Entry	8, 5-13	10, 6-17	0.0002

SLEDAI=Systemic lupus erythematosus activity index.

Table 3: Variables Associated with LDAS by Univariable analyses.

Characteristic	LDAS During Follow-Up Yes(N=314) [N (%) or median (25th – 75th percentiles)]	 No (N=588) [N (%) or median (25th – 75th percentiles)]	p-value
Sociodemographic Characteristics			
Gender			0.4250
Male	30 (9.6)	63 (10.7)	
Female	284 (90.4)	525 (89.3)	
Age at Diagnosis, years	28, 21-39	25, 19-34	0.0024
Age at First Symptom, years	27, 19-37	24, 18-33	0.0095
Age at Cohort Entry, years	28, 21-39	26, 20-34	0.0020
Ethnic Group			0.8450
Caucasian	141 (44.9)	227 (38.8)	
Mestizo	129 (41.1)	249 (42.6)	
African Latin American	37 (11.8)	84 (14.4)	
Other	7 (2.2)	25 (4.3)	
Socioeconomic Status			0.0099
High/Middle High	39 (12.5)	42 (7.1)	
Middle	97 (31.2)	156 (26.5)	
Middle Low/Low	175 (56.3)	390 (66.3)	
Residence			0.1767
Urban	291 (93.0)	526 (90.1)	
Rural	22 (7.0)	58 (9.9)	
Medical Coverage			0.3530
No Coverage	36 (11.5)	99 (16.9)	
Partial Coverage	83 (26.5)	144 (24.6)	
Full Coverage	194 (62.0)	342 (58.5)	
Education			0.0073
0-7 years	86 (27.9)	178 (31.9)	
8-12 years	134 (43.5)	266 (47.7)	
13 or more years	88 (28.6)	114 (20.4)	
Disease Duration at Cohort Entry			0.4751
Entered at Diagnosis	178 (56.7)	367 (62.4)	
Up to 6 Months	47 (15.0)	85 (14.5)	
6 to 12 months	38 (12.1)	63 (10.7)	
13 to 24 months	51 (16.2)	73 (12.4)	
Clinical Characteristics at Cohort Entry			

Characteristic	LDAS During Follow-Up: Yes(N=314) [N (%) or median (25th – 75th percentiles)]	LDAS During Follow-Up: No (N=588) [N (%) or median (25th – 75th percentiles)]	p-value
General manifestations	216 (68.8)	436 (74.1)	0.0065
Musculoskeletal involvement	294 (93.6)	519 (88.3)	0.2147
Mucocutaneous involvement	269 (85.7)	531 (90.3)	0.0365
Ocular involvement	35 (11.1)	47 (8.0)	0.2817
Lung involvement	10 (3.2)	30 (5.1)	0.0611
Cardiovascular involvement	89 (28.3)	209 (35.5)	0.0682
Renal involvement	108 (34.4)	290 (49.3)	0.0003
Neurologic involvement	56 (17.8)	125 (21.3)	0.4050
Hematological involvement	204 (65.0)	405 (68.9)	0.2707
Immunological involvement	197 / 251 (78.5)	386 / 474 (81.4)	0.2052
Treatments at Cohort Entry			
Antimalarials	108 (34.4)	171 (29.1)	0.2091
Prednisone (Higher dose before baseline)			0.0252
None	139 (44.3)	288 (49.0)	
Low (≤ 7.5 mg/d)	7 (2.2)	9 (1.5)	
Medium (>7.5 ≤15 mg/d)	40 (12.7)	43 (7.3)	
High (>15 <60 mg/d)	84 (26.8)	172 (29.3)	
Very High (≥ 60 mg/d)	44 (14.0)	76 (12.9)	
Immunosuppressive drugs	65 (20.7)	101 (17.2)	0.3585
Disease Status at Cohort Entry			
SLEDAI at Cohort Entry	8, 5-13	11, 6-17	< 0.0001

SLEDAI=Systemic lupus erythematosus activity index. SDI: SLICC/ACR damage index

Table 4: Predictors of Remission. Multivariable model.

Predictor	**Hazard ratio (95% CI)**	**p value**
Medical coverage		
No coverage	0.628 (0.375 – 1.052)	0.0774
Partial coverage	1.257 (0.908 – 1.740)	0.1675
Full coverage		Ref.
Absence of mucocutaneous manifestations*	1.571 (1.064 – 2.320)	0.0230
Absence of renal involvement*	1.487 (1.067 – 2.073)	0.0191
Absence of hematologic involvement*	1.354 (1.005 – 1.825)	0.0463
Immunosuppressive drugs use	1.468 (1.025 – 2.105)	0.0364
SLEDAI at cohort entry, per one unit decrease	1.028 (1.006 – 1.051)	0.0112

* Before or at cohort entry

Table 5: Predictors of LDAS. Multivariable model.

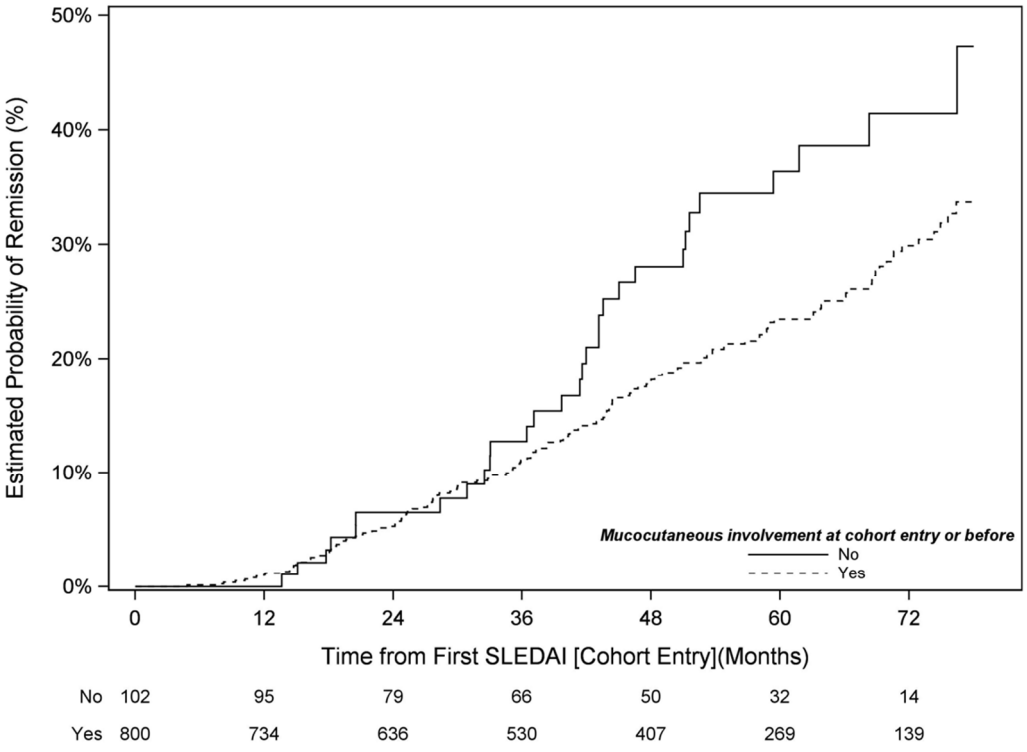
Predictor	Hazard ratio (95% CI)	p value
Age at cohort entry, per 5 years increase	1.050 (1.004 – 1.098)	0.0341
Absence of mucocutaneous manifestations*	1.401 (1.016 – 1.930)	0.0394
Absence of renal involvement*	1.344 (1.049 -1.721)	0.0194
SLEDAI at cohort entry, per one unit decrease	1.025 (1.009 – 1.042)	0.0027

* Before or at cohort entry

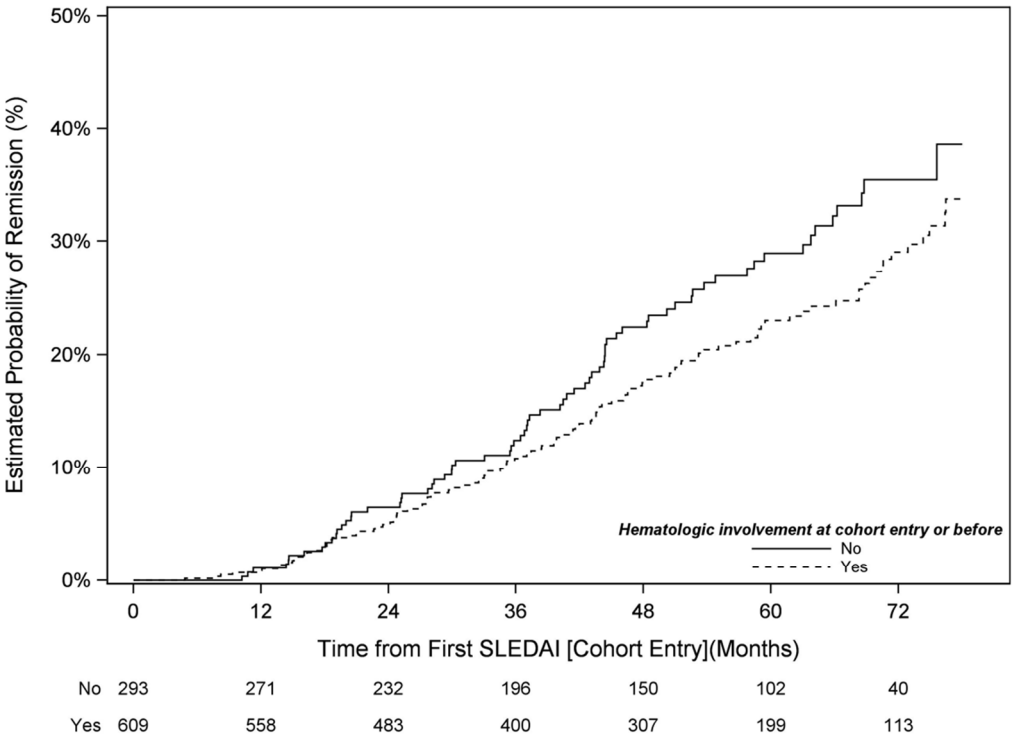
Figure Legends

Figure 1: Predictors of Remission in GLADEL Cohort

A: Presence of mucocutaneous involvement. B: Presence of hematologic involvement. C: Presence of renal involvement. D. Immunosuppressive drugs use. E. SLEDAI at baseline (categorized).



A



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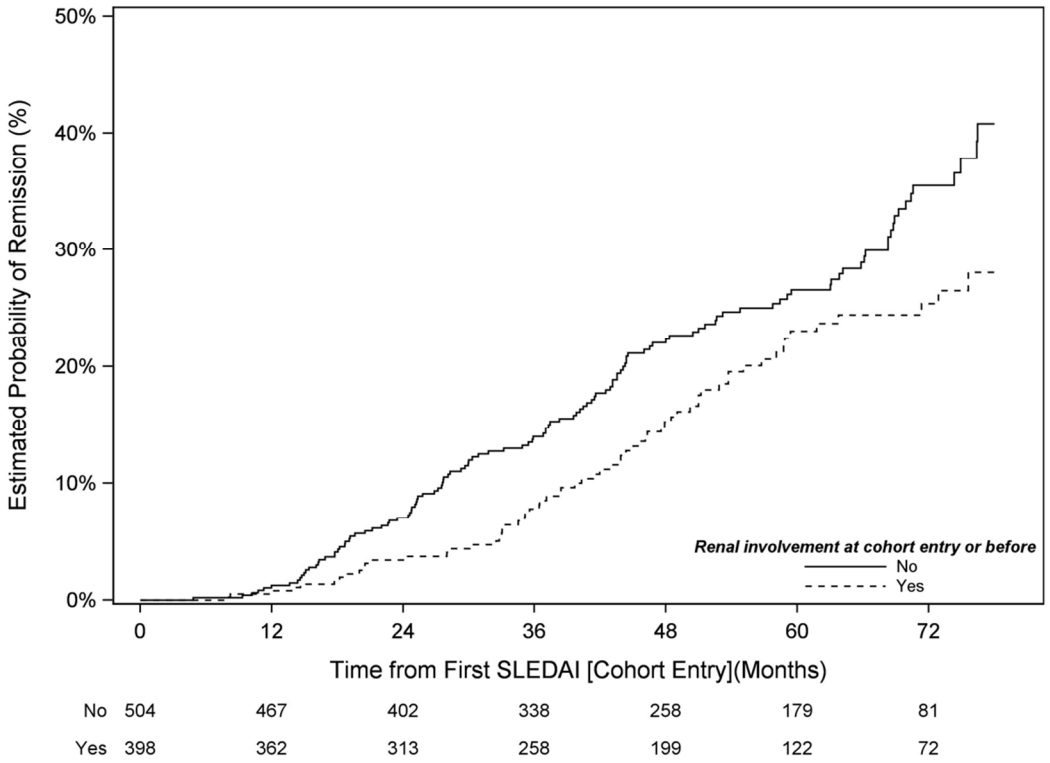

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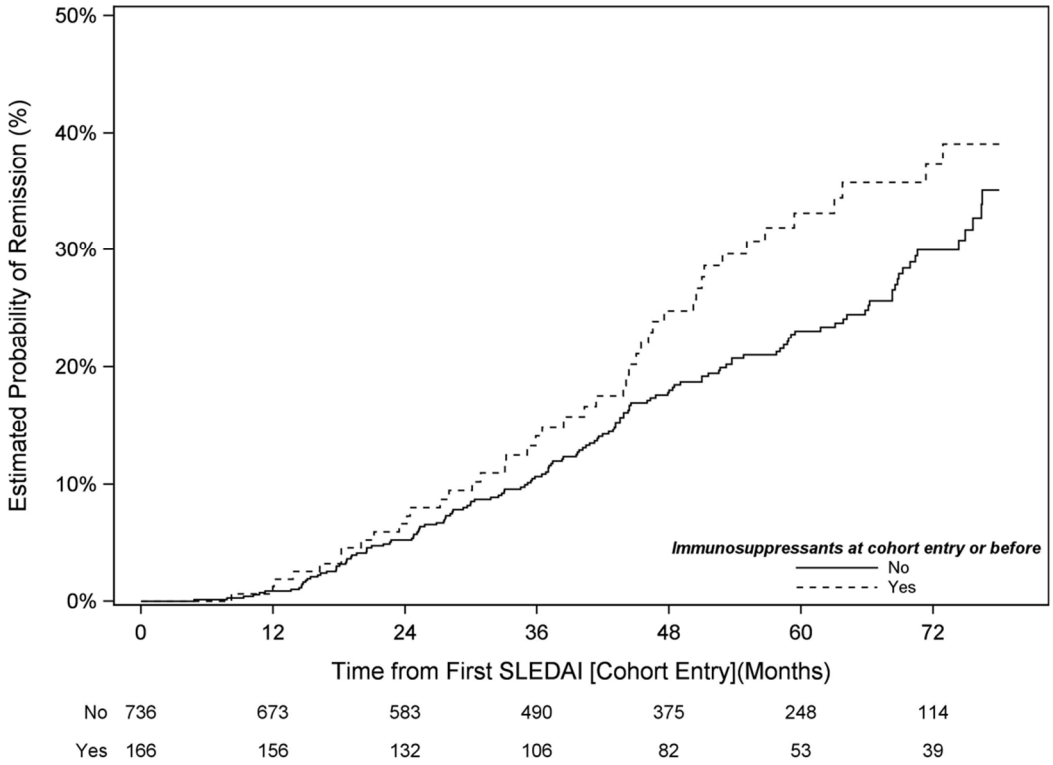

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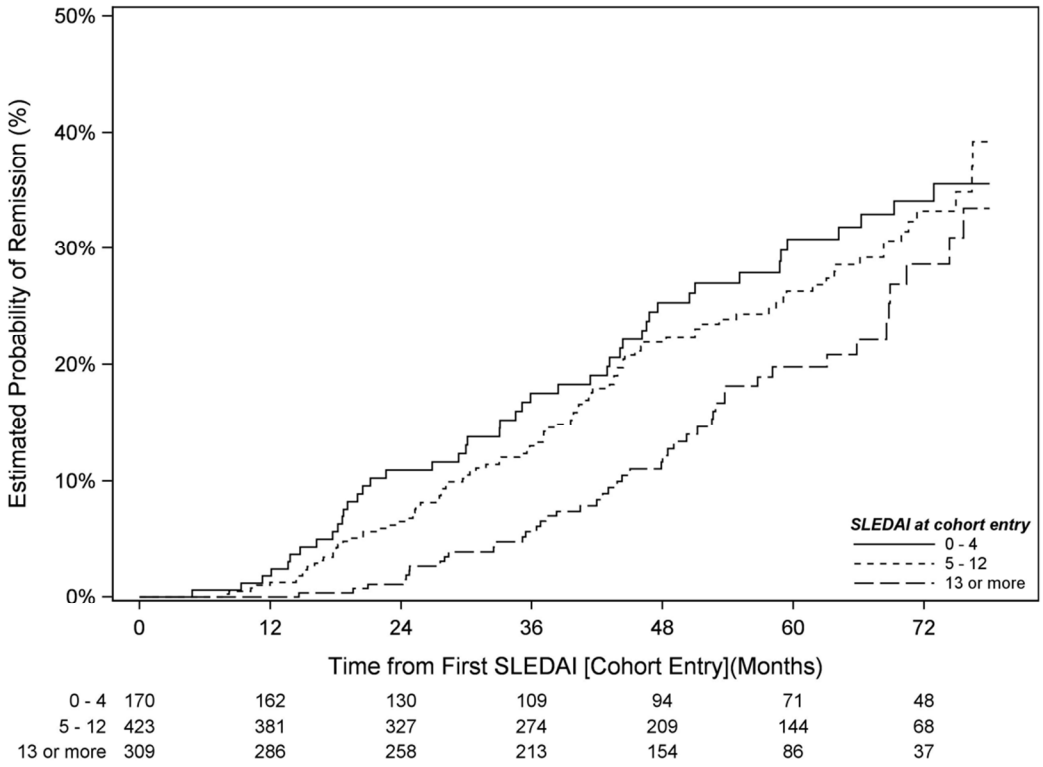

E
Figure 1