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Treatment patterns and outcomes of first lupus nephritis episode over 25 years in two Latin American cohorts

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Abstract

Objectives: To compare the treatments used for the first episode of lupus nephritis (LN) in two Latin American cohorts (historical and contemporary) over a 25-year period, and their associations with clinical outcomes.

Methods: Patients with biopsy-confirmed first LN episode were classified as non-proliferative (class V) or proliferative (classes III/IV). Sociodemographic, clinical, and treatment variables were described. Propensity score matching was used to examine the associations with four outcomes: mortality, damage accrual (SDI), hospitalization, and end-stage renal disease (ESRD).

Results: A total of 532 SLE patients were included: 362 from GLADEL 1.0 (historical cohort) and 170 from GLADEL 2.0. (contemporary). Compared to GLADEL 1.0, patients in GLADEL 2.0 received lower doses of oral glucocorticoids (GC), more frequently GC pulses and antimalarials but less frequently cyclophosphamide. An increase in the use of mycophenolate mofetil and other immunosuppressants was also observed. In the logistic regression models, SDI was associated with baseline SDI and GC pulses, whereas belonging to the GLADEL 2.0 was a protective factor. Mortality was associated with Mestizo ethnicity and partial health coverage; antimalarial was identified as a protective factor. Hospitalizations were associated with baseline SLEDAI and SDI, follow-up time, and lower educational level. Belonging to the GLADEL 2.0 cohort was protective against the occurrence of ESRD.

Conclusions: Patients in the contemporary cohort benefited from advances in treatment strategies, with less cumulative damage and progression to ESRD, although mortality remained unchanged. These improvements likely reflect the increased use of newer therapies, more targeted approaches, in line with current treatment guidelines, and better access to specialized care.

Keywords

lupus erythematosus systemic, lupus nephritis, treatment, epidemiology, Latin American

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Introduction

Systemic lupus erythematosus (SLE) is a complex and heterogeneous autoimmune disease.[1] Lupus nephritis (LN) is present in 7-31% of patients at diagnosis and in 31-48% of patients during the course of their disease.[2] Up to 20% of patients with LN will progress to end-stage renal disease (ESRD) within 10 years.[3] LN is observed more frequently and at a younger age in US Hispanics (Mestizos or of mixed European and Native American ancestry), African Americans and Asians than in Caucasian populations.[4–6]

In recent decades, there have been changes in the treatment of LN: inclusion of new therapeutics, a strong recommendation to use lower doses of glucocorticoids (GC) and data in favor of the universal use of antimalarials (AM). In this regard, the Latin American guidelines developed by the *Grupo Latino Americano De Estudio del Lupus* (GLADEL) and the *Panmerican League of Associations for Rheumatology (*PANLAR) have emphasized these recommendations.[7] In the treatment of LN, inclusion of new therapeutic options has broadened the horizons. The treat to target (T2T) approach is essential in the management of SLE patients; it is focused on the concept that disease modifications are conducive to a diminished probability of damage accrual.[8,9]

It can be hypothesized that changes in the treatment of LN may favorably influence several outcomes such as mortality, healthcare resource utilization, and damage accrual overall and, particularly damage in the renal domain. Thus, the objective of this study is to describe and compare the treatment of the first LN episode in two Latin American (LA) cohorts over a 25-year period and their relationship with the different outcomes noted.

Methods

The GLADEL 1.0 (historical cohort) is an observational, multiethnic, longitudinal inception cohort started in 1997 and constituted by patients from 34 centers from nine Latin American countries.[10] Initial patient enrollment began in October 1997. Patients were eligible for inclusion only if their SLE diagnosis occurred after January 1, 1996, as confirmed by a rheumatologist or an internist with expertise in SLE. Fulfillment of 4 of the 1982 ACR[11] SLE criteria at the time of enrollment was not mandatory but 79.5% patients met ≥4 criteria at diagnosis and 95.9% during the follow-up period. Patients included in this cohort had to have a disease duration ≤24 months.

GLADEL 2.0, on the other hand, is a contemporary observational cohort that includes both incident and prevalent LN cases, initiated in 2019.[12] Forty-four centers from 10 Latin-American countries enrolled patients ≥18 years who fulfilled the 1982/1997 American College of Rheumatology (ACR)[11,13] and/or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria.[14] SLE patients in this cohort were categorized into four different subsets, according to the presence of renal disease: patients with SLE, without renal involvement; patients with SLE, with prevalent renal involvement (at any time during their disease course), currently inactive; patients with SLE, with prevalent renal involvement (at any time during their disease course), currently active; and patients with SLE, with incident renal involvement (de novo).

For theses analysis, the first LN episode defined by histopathology according to the International Society of Nephrology and the Renal Pathology Society[15] was considered. It included two groups: non-proliferative (class V) and proliferative (III/IV) LN. Due to their low prevalence in both cohorts, classes I and II were excluded from the analysis. For the purpose of this study, only de novo incident LN were examined in GLADEL 2.0 (Figure 1).

The various therapeutic regimens used in both cohorts are described. In addition, sociodemographic variables including age at SLE diagnosis and at cohort entry, gender, ethnicity [Caucasian, Mestizo (of European and Native American ancestry), and African Latin American (ALA)], socioeconomic status [SES] (by the Graffar's method[16]), medical insurance (full vs partial/no coverage), and years of formal education were obtained. Clinical variables including ACR and non-ACR clinical manifestations and serological variables.

The SLE disease activity index (SLEDAI),[17] the presence of hospitalizations, new episode(s) of LN during the follow-up, the renal domain of the SLICC/ACR Damage Index (SDI)[18] (presence of at least one of the following: glomerular filtration rate <50%, proteinuria >3.5 g/24 h or ESRD) and mortality during the follow up, were examined. ESRD according to the SDI was assessed at the end of follow up.

This study is being conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH). The protocol has received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study at all participating centers. All patients signed the informed consent. Confidentiality of all participants is being maintained.

Statistical analyses

A descriptive cross-sectional analysis of data was performed comparing the cohorts with respect to sociodemographic and clinical variables, treatments and the four pre-defined outcomes: mortality, hospitalizations, ESRD and damage accrual on follow-up. Numeric variables are reported as medians (interquartile ranges IQR) and compared using Kruskall-Wallis test; categorical variables are reported as frequencies (percentages) and compared using either the Chi-square or the Fisher exact tests, as appropriate.

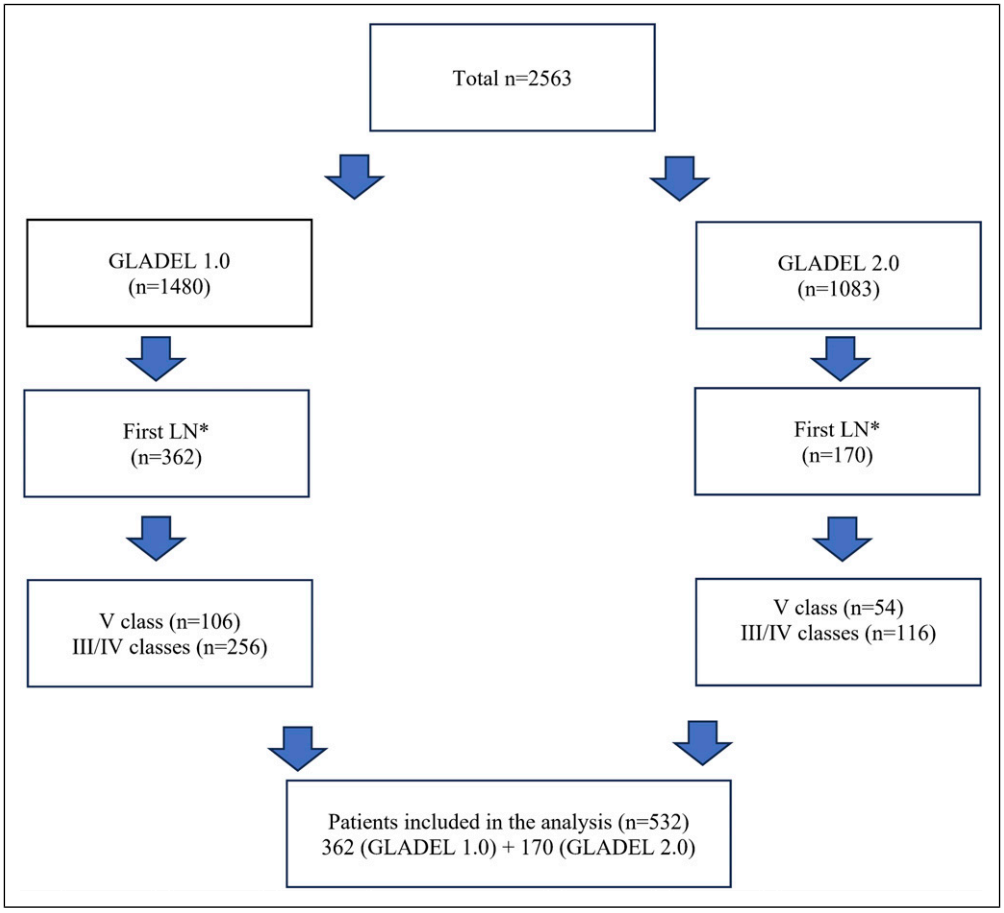

Figure 1. Flow diagram
LN: Lupus nephritis; * biopsy-confirmed.

Additionally, propensity score matching was used to compare the cohort effects on the outcomes of interest. The propensity scores were estimated using logistic regression adjusting by sociodemographic and clinical variables. One-to-one nearest neighborhood matching was applied based on gender, age at diagnosis, age at cohort entry, histological class, ethnicity, education level, SLEDAI and SDI at cohort entry and disease duration at cohort entry. Cluster-robust variance was used to estimate the standard error. Odds ratio (OR) and their respective 95% confidence intervals were calculated. As sensitivity analysis, GLADEL 1.0 patients were censored to match the follow-up duration of those in GLADEL 2.0. All reported *p*-values are two-tailed, with a probability level<0.05 indicating statistical significance. The collected data were analyzed using R software (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 532 SLE patients were included in the analysis, 362 patients from GLADEL 1.0 and 170 from GLADEL 2.0. SLE Patients in the GLADEL 2.0 cohort were older (31 [23.2-39.0] vs 26 [20.0-35.0] years old; $p = 0.001$), had a longer disease duration (4.2 [1.2-28.8] vs 1.1 [0-10.6] months; $p = 0.001$), were more frequently Mestizo (119 [70.0%] vs 178 [49.4%], $p = 0.001$), had a higher educational level (12 [11.0-15.2] vs 11 [7.0-13.0] years, $p = 0.001$), and had a lower full health care coverage (80 [48.2%] vs 227 [63.1%], $p = 0.001$) compared to those in the GLADEL 1.0 cohort. Regarding renal involvement, SLE patients in GLADEL 2.0 showed a higher frequency of nephrotic syndrome (83 [50.3%] vs 66 [18.2%], $p = 0.001$) and of persistent proteinuria >500 mg/day (166 [98.2%] vs 295 [81.5%], $p = 0.001$); they also had lower creatinine levels at the time of LN diagnosis (0.8 [0.7-1.2] vs 1.0 [0.8-1.4] mg/dl, $p = 0.001$), and more pronounced hypocomplementemia (162 [99.4%] vs 207 [57.2%], $p = 0.001$). At the time of LN diagnosis, patients in the GLADEL 2.0 group also had a higher SLEDAI (16 [12.0-21.8] vs 12 [6.0-20.0], $p = 0.001$) and a lower SDI (0 [0-0] vs 1.0 [0-2.0], $p = 0.001$). GLADEL 2.0 cohort patients had a shorter follow-up than those in the GLADEL 1.0 cohort (2.1 [1.0-3.0] vs 4.3 [2.4-5.9] years, $p = 0.001$); they also had accrued less damage overall (0 [0-1.0] vs 2.0 [1.0-3.0], $p = 0.001$), less renal

Table 1. Sociodemographic and clinical characteristics of LN patients from the GLADEL 1.0 and 2.0 cohorts.

Characteristic[a]	Total			Class V			Class III/IV		
	GLADEL 1.0 (N = 362)	GLADEL 2.0 (N = 170)	p-value	GLADEL 1.0 (N = 106)	GLADEL 2.0 (N = 54)	p-value	GLADEL 1.0 (N = 256)	GLADEL 2.0 (N = 116)	p-value[b]
Sociodemographic variables									
Gender female, n (%)	315 (87)	139 (81.8)	0.116	93 (87.7)	41 (75.9)	0.070	222 (86.7)	98 (84.5)	0.629
Age at cohort entry (years), median (IQR)	26 (20.0-35.0)	31 (23.2-39.0)	0.001	29 (23.0-37.8)	32 (26.2-41.2)	0.217	25 (19.8-32.0)	30 (23.0-38.2)	0.001
Ethnic group, n (%)			0.001			0.014			0.004
Caucasian	131 (36.4)	33 (19.4)		34 (32.4)	8 (14.8)		97 (38)	25 (21.6)	
Mestizo	178 (49.4)	119 (70.0)		50 (47.6)	40 (74.1)		128 (50.2)	79 (68.1)	
ALA	37 (10.3)	16 (9.4)		15 (14.3)	5 (9.3)		22 (8.6)	11 (9.5)	
Other	14 (3.9)	2 (1.2)		6 (5.7)	1 (1.9)		8 (3.1)	1 (0.9)	
Socioeconomic status, n (%)			0.239			0.310			0.470
High/high-middle	20 (5.5)	5 (3.4)		5 (4.7)	0 (0)		15 (5.9)	5 (5.1)	
Middle	117 (32.3)	58 (39.7)		41 (38.7)	22 (45.8)		76 (29.7)	36 (36.7)	
Middle-low/low	225 (62.2)	83 (56.8)		60 (56.6)	26 (54.2)		165 (64.5)	57 (58.2)	
Education level (years), median (IQR)	11 (7.0-13.0)	12 (11.0-15.0)	0.001	11 (7.0-13.0)	12 (9.0-14.0)	0.040	11 (7.0-12.0)	13 (11.0-16.0)	0.001
Health insurance coverage (full), n (%)	227 (63.1)	80 (48.2)	0.001	73 (69.5)	19 (37.3)	0.001	154 (60.4)	61 (53.0)	0.001
Clinical variables									
Disease duration (months), median (IQR)	1.1 (0-10.6)	4.2 (1.2-28.8)	0.001	0.5 (0-10.3)	3.9 (1.3-20.7)	0.001	1.4 (0-10.7)	4.6 (1.1-31.0)	0.001
Age at diagnosis (years), median (IQR)	26 (19.2-34.0)	27 (22.0-36.0)	0.025	28.5 (22.0-37.0)	29 (22.0-36.0)	0.909	25 (19.0-31.0)	26 (21.0-36.0)	0.007
Mucocutaneous domain, n (%)	299 (82.6)	139 (81.8)	0.808	86 (81.1)	48 (88.9)	0.261	213 (83.2)	91 (78.4)	0.311
Articular domain, n (%)	276 (76.2)	136 (80.0)	0.374	75 (70.8)	44 (81.5)	0.181	201 (78.5)	92 (79.3)	0.892
Serous domain, n (%)	114 (31.5)	64 (37.6)	0.169	37 (34.9)	19 (35.2)	1.000	77 (30.1)	45 (38.8)	0.121
Neuropsychiatric domain, n (%)	34 (9.4)	11 (6.5)	0.317	12 (11.3)	4 (7.4)	0.581	22 (8.6)	7 (6.1)	0.531
Hematological domain, n (%)	232 (64.1)	121 (71.2)	0.116	64 (60.4)	40 (74.1)	0.114	168 (65.6)	81 (69.8)	0.476
Serological domain[c], n (%)	325 (100)	169 (100)		97 (100)	53 (100)		228 (100)	116 (100)	
Comorbidities, [d] n (%)	126 (34.8)	49 (36.6)	0.751	27 (25.5)	11 (28.9)	0.673	99 (38.7)	38 (39.6)	0.903
SLEDAI, median (IQR) baseline	12 (6.0-20.0)	16 (12.0-21.8)	0.001	11 (6.0-18.0)	14.5 (10.0-19.5)	0.055	12 (6.0-20.0)	17 (12.0-22.0)	0.001
SDI, median (IQR) baseline	1.0 (0-2.0)	0 (0-0)	0.001	1.0 (0-2.0)	0 (0-1.0)	0.001	1 (0-2.0)	0 (0-0)	0.001
Hypocomplementemia[e], n (%)	207 (57.2)	162 (99.4)	0.001	49 (46.2)	49 (98.0)	0.001	158 (61.7)	113 (100)	0.001
Antiphospholipid antibodies[f],n (%)	96 (26.5)	27 (24.8)	0.804	28 (26.4)	11 (32.4)	0.515	68 (26.6)	16 (21.3)	0.451
Persistent proteinuria >500 mg/day, n (%)	295 (81.5)	166 (98.2)	0.001	77 (72.6)	53 (98.1)	0.001	218 (85.2)	113 (98.3)	0.001
Nephrotic proteinuria, n (%)	66 (18.2)	83 (50.3)	0.001	17 (16.0)	27 (52.9)	0.001	49 (19.1)	56 (49.1)	0.001
Baseline creatinine, median (IQR)	1.0 (0.8-1.4)	0.8 (0.7-1.2)	0.001	0.8 (0.7-1.1)	0.8 (0.6-1.0)	0.194	1.0 (0.8-1.5)	0.9 (0.7-1.3)	0.005

[a]The frequency of each variable is calculated by excluding missing data.
[b]p-value corresponding to the Wilcoxon Test or Fisher's Exact Test as appropriate; IQR: interquartile range; ALA: African Latin American; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Index.
[c]Presence of at least one of the following: ANA positive, Anti DNA positive and/or Anti Sm positive.
[d]Presence of at least one of the following: diabetes, hypertension or dyslipidemia.
[e]Presence of at least one of the following: low C3 and/or C4 and/or CH50.
[f]Presence of at least one of the following: Positive anticardiolipin or lupus anticoagulant or anti-glycoprotein b2 antibodies; LN: Lupus nephritis.

Table 2. Follow up variables of LN patients from the GLADEL 1.0 and GLADEL 2.0 cohorts.

Characteristic[a]	Total			Class V			Class III/IV		
	GLADEL 1.0 (N = 362)	GLADEL 2.0 (N = 170)	p-value	GLADEL 1.0 (N = 106)	GLADEL 2.0 (N = 54)	p-value	GLADEL 1.0 (N = 256)	GLADEL 2.0 (N = 116)	p-value[b]
Follow up variables									
Time to follow-up (years), median (IQR)	4.3 (2.4-5.9)	2.1 (1-3)	0.001	4.3 (2.1-5.4)	1.4 (0.5-2.7)	0.001	4.4 (2.7-6)	2.2 (1.2-3)	0.001
SDI at the end of follow-up, median (IQR)	2 (1-3)	0 (0-1)	0.001	2 (1-3)	0 (0-1)	0.001	2 (1-4)	0 (0-1)	0.001
Renal SDI[c] at the end of follow-up, median (IQR)	1 (1-2)	0 (0-0)	0.001	1 (1-2)	0 (0-0)	0.001	1 (1-2)	0 (0-0)	0.001
New episode of LN during the follow-up, n (%)	57 (15.7)	23 (13.5)	0.603	18 (17)	13 (24.1)	0.297	39 (15.2)	10 (8.6)	0.098
Mortality at the end of follow-up, n (%)	28 (7.7)	7 (4.1)	0.135	5 (4.7)	2 (3.7)	1.000	23 (9)	5 (4.3)	0.139
Hospitalizations during the follow up, n (%)	312 (86.2)	136 (80)	0.075	91 (85.8)	43 (79.6)	0.366	221 (86.3)	93 (80.2)	0.164
ESRD at the end of follow-up, n (%)	44 (12.2)	4 (2.4)	0.001	4 (3.8)	0 (0)	0.301	40 (15.6)	4 (3.4)	0.001

[a]The frequency of each variable is calculated by excluding missing data.
[b]p-value corresponding to the Wilcoxon Test or Fisher's Exact Test as appropriate; IQR: interquartile range.
[c]Presence of at least one of the following: glomerular filtration rate <50%, proteinuria >3.5 gm/24 h or ESRD (End-Stage Renal Disease); LN: Lupus nephritis.

damage (0 [0-0] vs 1.0 [1.0-2.0], p = 0.001), and less ESRD (4 [2.4%] vs 44 [12.2%], p = 0.001). The comparisons related to the histological classes are described in Tables 1 and 2.

SLE patients included in GLADEL 2.0 had received lower oral GC (143 [84.1%] vs 358 [98.9%], p = 0.001) with a lower oral GC cumulative dose (5.4 [3.0-10.3] vs 8.5 [3.9-16.4] gr, p = 0.001), and higher use of GC bolus (100 [58.8%] vs 135 [37.3%], p = 0.001), but with a lower cumulative dose (1.5 [1.5-3.0] vs 2.0 [1.0-3.0] gr, p = 0.216). SLE patients in GLADEL 2.0 used antimalarials (AM) more frequently than those in GLADEL 1.0 (165 [97.1%] vs 267 [73.8%], p = 0.001); moreover, the use of hydroxychloroquine was also significantly higher (155 [91.2%] vs 141 [39.0%], p = 0.001); in contrast, they used cyclophosphamide less often (80 [47.1%] vs 287 [79.3%], p = 0.001). In GLADEL 2.0, an increase in the use of mycophenolate mofetil, and to a lesser extent of belimumab and rituximab, was noted over time. In contrast, the use of cyclosporin A decreased in GLADEL 2.0 (2 [1.2%] vs 18.0 [5%], p = 0.047; Table 3).

Regarding damage accrual, logistic regression analysis using propensity score matching showed that baseline SDI (OR 1.26, [CI 95% 1.16-1.36], p = 0.001) and GC bolus use (OR 1.16, [CI 95% 1.03-1.29], p = 0.016) were associated with damage accrual, whereas belonging to the GLADEL 2.0 cohort was protective (OR 0.76, [CI 95% 0.65-0.91], p = 0.020). Mestizo ethnicity (OR 1.07 [CI 95% 1.01-1.13], p = 0.018) and partial health insurance coverage were associated with mortality (OR 1.2, [CI 95% 1.02-1.43], p = 0.026); conversely, antimalarials use was identified as a protective factor (OR 0.89, [CI95% 0.71-0.99], p = 0.043; Table 4). The baseline SLEDAI (OR 1.01 [CI95% 1.01-1.01], p = 0.032), SDI (1.05 [CI 95% 1.01-1.13], p = 0.028), and follow-up time (OR 1.07 [CI 95% 1.01-1.12], p = 0.003) were significantly associated with hospitalizations whereas education level was protective (OR 0.98 [CI 95% 0.97-0.99, p = 0.034). Finally, belonging to the GLADEL 2.0 cohort was a protective factor for the development of ESRD (OR 0.87 [CI 95% 0.74-0.99], p = 0.039; Table 5).

Following the sensitivity analysis that accounted for differences in follow-up duration between cohorts, the most relevant findings remained unchanged, further supporting the robustness of the results (Supplemental Tables 1 and 2).

Discussion

To our knowledge, this is the first study comparing SLE patients over the course of more than two decades in relation to their first LN episode, the treatments received and primary health outcomes.

Over the past 25 years, we have observed an increase in ethnic diversity in Latin America overall; this translates into a higher proportion of Mestizo patients in the GLADEL 2.0 cohort.[19,20] Notably, patients now have a higher level of

Table 3. Treatment of LN patients in the GLADEL 1.0 and 2.0 cohorts.

Characteristic[a]	Total			Class V			Class III/IV		
	GLADEL 1.0 (N = 362)	GLADEL 2.0 (N = 170)	p-value	GLADEL 1.0 (N = 106)	GLADEL 2.0 (N = 54)	p-value	GLADEL 1.0 (N = 256)	GLADEL 2.0 (N = 116)	p-value[b]
Oral glucocorticoid, n (%)	358 (98.9)	143 (84.1)	0.001	106 (100)	42 (77.8)	0.001	252 (98.4)	101 (87.1)	0.001
Oral glucocorticoid, cumulative dose (g), median (IQR)	8.5 (3.9-16.4)	5.4 (3.0-10.3)	0.001	7.9 (3.7-15.4)	4.2 (2.5-9.8)	0.005	8.9 (4-17.3)	5.8 (3.4-10.9)	0.005
Bolus glucocorticoid, n (%)	135 (37.3)	100 (58.8)	0.001	26 (24.5)	23 (42.6)	0.029	109 (42.6)	77 (66.4)	0.001
Bolus, cumulative dose (g), median (IQR)	2.0 (1.0-3.0)	1.5 (1.5-3.0)	0.216	1.0 (0.8-1.9)	1.5 (1.5-3.0)	0.042	2.0 (1.0-3.0)	1.5 (1.5-3.0)	0.216
Antimalarials, n (%)	267 (73.8)	165 (97.1)	0.001	87 (82.1)	52 (96.3)	0.012	180 (70.3)	113 (97.4)	0.001
IV cyclophosphamide, n (%)	287 (79.3)	80 (47.1)	0.001	58 (54.7)	21 (38.9)	0.067	229 (89.5)	59 (50.9)	0.001
Mycophenolate mofetil, n (%)	-	123 (72.4)		-	33 (61.1)		-	90 (77.6)	
Tacrolimus, n (%)	0 (0)	13 (7.6)		-	4 (7.4)		-	9 (7.8)	
Cyclosporin A, n (%)	18 (5.0)	2 (1.2)	0.047	2 (1.9)	2 (3.7)	0.604	16 (6.2)	-	0.004
Belimumab, n (%)	-	6 (3.5)		-	0 (0)		-	6 (5.2)	
Rituximab, n (%)	-	18 (10.6)		-	8 (14.8)		-	10 (8.6)	

[a]The frequency of each variable is calculated by excluding missing data.
[b]p-value corresponding to the Wilcoxon Test or Fisher's Exact Test as appropriate; IQR: interquartile range; IV: intravenous.

Table 4. Impact of treatment on damage accrual and mortality adjusting for sociodemographic and clinical variables: Multivariable logistic regression using the Propensity Score Matching[b].

	Damage accrual		Mortality	
Variable	OR (95%CI)	p-value	OR (95%CI)	p-value
Gender	1.09 (0.96, 1.30)	0.308	0.94 (0.86, 1.03)	0.194
Female (Ref)				
Male				
Age at cohort entry[a]	1.10 (0.93, 1.3)	0.216	0.95 (0.84, 1.18)	0.368
Age at diagnosis[a]	0.90 (0.76, 1.07)	0.189	1.05 (0.93, 1.19)	0.357
Ethnic group	0.98 (0.82, 1.16)	0.864	1.07 (1.01, 1.13)	0.018
Caucasian (Ref)	1.04 (0.87, 1.25)	0.677	1.09 (0.97, 1.23)	0.116
Mestizo	1.05 (0.85, 1.30)	0.638	1.01 (0.90, 1.12)	0.894
ALA				
Other				
GLADEL cohort	0.76 (0.65, 0.91)	0.02	1.19 (0.99, 1.28)	0.099
1.0 (Ref)				
2.0				
Histopathology class	0.94 (0.84, 1.06)	0.311	1.01 (0.92, 1.11)	0.786
II/IV(Ref)				
III/IV				
Education level	1.00 (0.99, 1.03)	0.490	0.99 (0.97, 1.01)	0.070
Health insurance coverage	0.86 (0.99, 1.07)	0.168	1.21 (1.02,1.43)	0.026
Without (Ref)	0.97 (0.82,1.15)	0.706	0.98 (0.91, 1.1)	0.679
Partial				
Full				
Socioeconomic status	0.89 (0.66, 1.21)	0.467	0.89 (0.77,1.04)	0.134
High/high-middle (Ref)	1.10 (1.01, 1.09)	0.546	0.89 (0.74,1.07)	0.204
Middle				
Middle-low/low				
SLEDAI baseline[a]	1.11 (0.99, 1.01)	0.720	1.00 (0.99, 1.01)	0.723
SDI baseline[a]	1.26 (1.176, 1.36)	0.001	1.03 (0.98, 1.08)	0.291
Disease duration[a]	0.99 (0.98, 1.01)	0.217	1.00 (0.99, 1.01)	0.478
Comorbidities	1.05 (0.93, 1.19)	0.457	0.98 (0.92, 1.04)	0.518
Follow up duration[a]	1.01 (0.96, 1.06)	0.799		
Creatinine baseline[a]	1.01 (0.97, 1.06)	0.630	1.01 (0.96, 1.07)	0.608
Hospitalizations	1.06 (0.94, 1.21)	0.337	0.98 (0.91, 1.06)	0.610
New episode of LN	0.97 (0.88, 1.14)	0.754	1.07 (0.85, 1.36)	0.550
SDI at the end of follow-up[a]			1.04 (0.99, 1.07)	0.063
Renal SDI[c] at the end of follow-up[a]			1.00 (0.94, 1.07)	0.985
ESRD at the end of follow-up			0.99 (0.71, 1.30)	0.960
Mortality at the end of follow-up	0.92 (0.76, 1.15)	0.450		
Antimalarials use	1.05 (0.90, 1.23)	0.518	0.89 (0.75, 1.07)	0.211
Oral glucocorticoid use	1.03 (0.83, 1.28)	0.776	1.00 (1.00, 1.01)	0.628
Bolus glucocorticoid use	1.16 (1.03, 1.29)	0.016	1.06 (0.99, 1.14)	0.097
IV cyclophosphamide	1.09 (0.89,1.23)	0.266	1.02 (0.92, 1.09)	0.600

OR: Odd Ratio; CI: Confidence Interval.

[a]Increase per 1 unit. Ref: Reference; ESRD: End-Stage Renal Disease; ALA: African Latin American; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Index; LN: Lupus nephritis.

[b]Matching was applied based on gender, age at diagnosis, age at cohort entry, histopathology class, ethnicity, education level, SLEDAI and SDI at cohort entry and disease duration at cohort entry.

[c]Presence of at least one of the following: Glomerular filtration rate <50%, proteinuria >3.5 gm/24 h or ESRD.

education, reflecting improved access to educational opportunities.[21] Conversely, full health coverage across the region has declined, bringing to light persistent structural challenges such as poverty and inequality, particularly in terms of health.[22,23,24]

Regarding LN, patients now present more frequently with proteinuria and lower creatinine levels. This may reflect greater access to multidisciplinary care, improved monitoring and systematic screening for renal involvement in lupus patients, particularly among Mestizos in LA. These

Table 5. Impact of treatment patterns on hospitalizations and ESRD adjusting for sociodemographic and clinical variables: Logistic regression using Propensity Score matching[b].

	Hospitalizations		ESRD	
Variable	OR (95%CI)	p-value	OR (95%CI)	p-value
Gender female (Ref) male	0.96 (0.83, 1.11)	0.625	1.02 (0.91, 1.14)	0.720
Age at cohort entry[a]	1.02 (0.88, 1.22)	0.671	0.95 (0.88, 1.04)	0.575
Age at diagnosis[a]	0.96 (0.84, 1.16)	0.655	1.05 (0.96, 1.14)	0.610
Ethnic group caucasian (Ref)	1.10 (0.9, 1.35)	0.335	1.07 (0.93, 1.07)	0.958
Mestizo	0.74 (0.57, 0.96)	0.024	1.05 (0.9, 1.14)	0.833
ALA	0.78 (0.42, 1.45)	0.430	0.96 (0.77, 1.19)	0.679
Other				
GLADEL cohort	1.18 (0.96, 1.48)	0.115	0.87 (0.74, 0.99)	0.039
1.0 (Ref)				
2.0				
Histopathology class	0.92 (0.81, 1.05)	0.205	1.05 (0.99, 1.11)	0.118
V (Ref)				
III/IV				
Education level	0.98 (0.97, 0.99)	0.034	1.01 (0.99, 1.01)	0.775
Health insurance coverage	1.04 (0.87,1.24)	0.666	1.12 (0.97, 1.29)	0.124
Without (Ref)	1.03 (0.97,1.01)	0.588	1.06 (0.97, 1.15)	0.215
Partial				
Full				
Socioeconomic status	1.25 (0.71,2.21)	0.469	1.01 (0.89, 1.19)	0.941
High/high-middle (Ref)	1.23 (0.70,2.19)	0.445	1.00 (0.99, 1.10)	0.713
Middle				
Middle-low/low				
SLEDAI baseline[a]	1.01 (1.01, 1.01)	0.032	1.00 (0.99, 1.00)	0.252
SDI baseline[a]	1.05 (1.01, 1.13)	0.028	1.00 (0.93, 1.07)	0.877
Disease duration[a]	1.00 (0.98, 1.01)	0.584	1.00 (1.00, 1.01)	0.664
Comorbidities	0.95 (0.84, 1.06)	0.745	1.08 (0.98, 1.19)	0.137
Duration of follow up[a]	1.07 (1.01, 1.12)	0.003	0.98 (0.96, 1.00)	0.129
Creatinine at baseline[a]	1.02 (1.00, 1.04)	0.083	1.00 (0.98, 1.03)	0.754
Hospitalizations			1.02 (0.94, 1.10)	0.753
New episode of LN	1.02 (0.87, 1.20)	0.902	0.95 (0.86, 1.06)	0.402
SDI at the end of follow-upa	0.99 (0.94, 1.05)	0.795	1.02 (0.95, 1.50)	0.604
Renal SDI[c,a] at the end of follow-up	1.03 (0.93, 1.13)	0.587		
ESRD at the end of follow-up	1.07 (0.73, 1.57)	0.725		
Mortality at the end of follow-up	0.93 (0.76, 1.14)	0.480	1.11 (0.92, 1.48)	0.438
Antimalarials use	1.03 (0.89, 1.43)	0.628	0.98 (0.85, 1.10)	0.317
Oral glucocorticoid use	0.94 (0.76, 1.11)	0.635	1.12 (0.94, 1.33)	0.209
Bolus glucocorticoid use	0.99 (0.89, 1.11)	0.887	1.09 (0.99, 1.20)	0.079
IV cyclophosphamide use	1.06 (0.94,1.20)	0.327	1.03 (0.98,1.08)	0.467

OR: Odd Ratio; CI: Confidence Interval; Ref: Reference; ESRD: End-Stage Renal Disease; ALA: African Latin American; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Index.
[a]Increase per 1 unit.
[b]Matching was applied based on gender, age at diagnosis, age at cohort entry, histopathology, ethnicity, education level, SLEDAI and SDI at cohort entry and disease duration at cohort entry.
[c]Presence of at least one of the following: Glomerular filtration rate <50%, proteinuria >3.5 gm/24 h or ESRD (End-Stage Renal Disease); LN: Lupus nephritis.

findings may also be linked to the lower baseline and long-term damage accrual observed in these patients. GLADEL's contributions to the understanding of lupus in Latin America have encouraged physicians to manage patients more closely, with efforts directed towards the early diagnosis of LN and the timely initiation of treatment,.[7,10] Additionally, a higher frequency of hypocomplementemia has been noted, which could be attributed to improved access to quality-certified laboratories.

Based on the experience and key findings from GLADEL 1.0, such as the more aggressive disease presentation with greater renal involvement in Mestizo

patients and the protective effect of AM against the development of LN, we can affirm that these lessons have been incorporated into clinical practice.[6,7,10,25–28] In GLADEL 2.0, 97.1% of patients are receiving AM compared to 73.8% in GLADEL 1.0, while the use of oral GC has decreased, along with its cumulative dose. Although the use of intravenous GC bolus has increased, the cumulative dose has been reduced, and the use of cyclophosphamide has declined by more than half. These findings indicate that physicians, to a large extent, are following both local and international treatment guidelines, emphasizing the broader use of AM and the strategy of minimizing GC exposure.[7,28,29] Mycophenolate mofetil has emerged as the most commonly used treatment for LN, particularly in patients with histological class III–IV, in accordance with current recommendations.[7,28,29]

During the follow-up period, patients in the GLADEL 2.0 cohort accrued less damage, both overall and specifically in the renal domain, and ESRD occurred less frequently. Although follow-up time in GLADEL 2.0 was approximately half that of GLADEL 1.0, these differences remained significant in propensity score adjusted logistic regression models and were further confirmed by sensitivity analyses accounting for comparable follow-up duration between patients in both cohorts.

Consistent with previous findings from GLADEL 1.0, hospitalizations were associated with higher baseline disease activity, baseline damage, and longer duration of follow-up.[30] In contrast, educational level emerged as the only protective factor. These findings underscore the critical role of socioeconomic variables in our patient outcomes. GLADEL has previously documented the impact of sociodemographic factors, such as low socioeconomic status, limited health coverage, lower educational level, and rural residence, on the development of LN and poorer outcomes.[6,10,21,27,31–33] Similar associations have also been reported in other lupus studies.[34–40] According to the World Health Organization,[41] social determinants are defined as 'the conditions in which people are born, grow, work, live, and age.' These factors account for between 30% and 55% of health outcomes and disproportionately affect individuals with low SES levels and those belonging to ethnic minorities.[42,43,44] In the context of lupus, the study of social determinants has been extensively developed, underscoring their relevance in culturally and ethnically diverse populations, as exemplified by the GLADEL cohort in LA.[45,46]

In this study, consistent with previous GLADEL findings, Mestizo ethnicity was associated with higher mortality.[10,27] This is a critical concern, given that 70% of patients with LN in the GLADEL 2.0 cohort were Mestizos. Similarly, several studies have demonstrated the significant impact of Mestizo ethnicity on poorer outcomes in lupus patients across LA and other geographic regions.[46,47] Belonging to certain ethnic groups may serve as a proxy for underlying socioeconomic disparities and restricted access to healthcare services; in line with this interpretation, partial health insurance coverage was independently associated with higher mortality during follow-up. These findings highlight the urgent need for targeted action, emphasizing comprehensive care and systematic screening for renal involvement from the time of lupus diagnosis in this population.

Another relevant finding was the use of antimalarials was found to be a protective survival factor in our patients. This observation is consistent with previous reports from GLADEL and other center highlighting the beneficial role of antimalarial therapy in improving patient outcomes.[6,26,27,48–50] Given their wide availability, low cost, and favorable safety profile, antimalarials remain a cornerstone of lupus management and a key strategy to improve patient survival, particularly in resource-limited settings.

These findings highlight the urgent need for targeted action, emphasizing comprehensive care and systematic screening for renal involvement from the time of lupus diagnosis in this population.

Although belonging to the GLADEL 2.0 cohort was associated with less damage accrual and progression to ESRD, mortality was comparable in both cohorts. This apparent dissociation may reflect the influence of other drivers of mortality in SLE, including infections, cardiovascular events, and late referral to specialized care, which could not be fully captured in the present analysis. While cardiovascular comorbidities were considered and did not differ between cohorts, residual confounding related to these and other unmeasured factors may partly explain the lack of observed differences in mortality. Accordingly, this finding should be interpreted with caution and is acknowledged as a limitation of the study.

This study has both strengths and limitations. Among the strengths is the reflection of paradigm shifts in lupus management, globally, and particularly within LA. These findings illustrate how such changes have positively impacted patient outcomes, even amidst ongoing challenges in accessing care and economic constraints across the region. Despite these obstacles, patients in LA have experienced tangible benefits during the study period. The main limitations include the inherent issues of historical analyses, such as missing data, patient inclusion/loss to follow-up during the COVID-19 pandemic in GLADEL 2.0, the lack of standardized data collection between cohorts, and the absence of specific variables that prevented assessment of renal response in GLADEL 1.0.

In conclusion, the time elapsed between these two cohorts has been beneficial for our SLE patients, particularly in reducing cumulative damage and progression to ESRD. The adoption of new therapeutic options, alongside a clear

reduction in GC use, underscores significant progress in clinical practice. Moving forward, our challenge is to improve equitable access to healthcare, ensuring that all patients have equal opportunities for successful outcomes. At GLADEL, we remain committed to this goal by raising awareness of the burden of lupus in LA and promoting continuing education initiatives for both physicians and patients.

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Supplemental material

Supplemental material for this article is available online.

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