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Central nervous system involvement in systemic lupus erythematosus: Data from the Spanish Society of Rheumatology Lupus Register (RELESSER)

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ABSTRACT

Objectives: To analyze the prevalence, incidence, survival and contribution on mortality of major central nervous system (CNS) involvement in systemic lupus erythematosus (SLE).
Methods: Patients fulfilling the SLE 1997 ACR classification criteria from the multicentre, retrospective RELESSER-TRANS (Spanish Society of Rheumatology Lupus Register) were included. Prevalence, incidence and survival rates of major CNS neuropsychiatric (NP)-SLE as a group and the individual NP manifestations cerebrovascular disease (CVD), seizure, psychosis, organic brain syndrome and transverse myelitis were calculated. Furthermore, the contribution of these manifestations on mortality was analysed in Cox regression models adjusted for confounders.
Results: A total of 3591 SLE patients were included. Of them, 412 (11.5%) developed a total of 522 major CNS NP-SLE manifestations. 61 patients (12%) with major CNS NP-SLE died. The annual mortality rate for patients with and without ever major CNS NP-SLE was 10.8% vs 3.8%, respectively. Individually, CVD (14%) and organic brain syndrome (15.5%) showed the highest mortality rates. The 10% mortality rate for patients with and without ever major CNS NP-SLE was reached after 12.3 vs 22.8 years, respectively. CVD (9.8 years) and organic brain syndrome (7.1 years) reached the 10% mortality rate earlier than other major CNS NP-SLE manifestations. Major CNS NP-SLE (HR 1.85, 1.29–2.67) and more specifically CVD (HR 2.17, 1.41–3.33) and organic brain syndrome (HR 2.11, 1.19–3.74) accounted as independent prognostic factors for poor survival.
Conclusion: The presentation of major CNS NP-SLE during the disease course contributes to a higher mortality, which may differ depending on the individual NP manifestation. CVD and organic brain syndrome are associated with the highest mortality rates.

Introduction

Neuropsychiatric systemic lupus erythematosus (NP-SLE) is a generic term referring to a series of neurological and psychiatric manifestations directly related to systemic lupus erythematosus (SLE), which usually represents either underlying inflammation or ischemia [1].

Central nervous system (CNS) involvement in SLE leads to a mosaic of clinical presentations ranging from non-specific minor symptoms (i.e. headache, mild cognitive dysfunction and depression) to major CNS NP-SLE including some of the most severe SLE manifestations [2,3]. Due to its low prevalence and its heterogeneity, NP-SLE has been frequently investigated as a composite endpoint. Previous studies include different proportions of patients with one or more of the nineteen NP-SLE manifestations as proposed in the NP-SLE American college of Rheumatology (ACR) nomenclature, which avoids to draw strong conclusions about the long-term outcomes and other aspects of the individual NP-SLE manifestations [4,5].

Both clinical outcomes and patient reported outcomes are known to be markedly affected in patients with NP-SLE [6,7]; it may be thus hypothesized that the presentation of major CNS NP-SLE manifestations has a negative impact on survival. However, previous studies on this topic provide controversial results. The standardized mortality ratio for SLE compared to the general population is around three and rises to a 10-fold increase in mortality in patients with NP-SLE [8,9]. On the other hand, other studies have shown that NP-SLE manifestations or NP-damage are not independent contributors to mortality in SLE [10]. These inconsistencies in the literature might be explained by the small number of NP-SLE patients included in the cohorts, differences in the NP-SLE definition used and the different proportion of patients with one or another NP-SLE manifestation included in the study. There is still a need for additional research on long-term outcomes and mortality attributed to major CNS NP-SLE in large cohorts of patients with SLE.

We aimed to analyze the prevalence and incidence of major CNS NP-SLE in a large and well-defined Spanish multicentre SLE cohort. We also investigated the survival of SLE patients developing major CNS NP-SLE manifestations and analysed the independent explanatory effect of these manifestations on mortality. Furthermore, the causes of death of these patients were also evaluated.

Methods

Study design and data source

This was a multicentre, retrospective study using data from the RELESSER (Registry of Systemic Lupus Erythematosus Patients of the Spanish Society of Rheumatology [SER]). RELESSER is a nationwide clinical register including data from patients with SLE (18 years or older) followed in one of the forty-five participating centres. This registry consists of two stages: the first one (RELESSER-TRANS) is a cross-sectional study with data being collected retrospectively with the main objective of describing the clinical characteristics and comorbidities of patients with SLE in Spain; the second stage (RELESSER-PROS) is a prospective study still ongoing, in which patients are followed over a period of nine years. For the present study, we only used data from the RELESSER-TRANS, which included a comprehensive assessment per patient retrospectively recorded by the treating rheumatologist until the last available visit to the rheumatologist or until the patient died. In case of death, the date and, when possible, the cause of death were also collected. Sociodemographic data, cumulative clinical and laboratory characteristics as well as comorbidities were collected. The investigators of all participating centres were trained before starting with data collection to ensure homogeneity in the reported variables. The methodology of RELESSER-TRANS including the different procedures applied to minimize missing data (<5% in 92% of the variables collected) and to ensure data quality are reported in detail elsewhere [11]. All participants gave written informed consent and their records were anonymized prior to analysis. Only patients fulfilling the ACR 1982 revised criteria for SLE were included in our study [12,13]. RELESSER-TRANS was approved by the institutional Ethics Committee of the Hospital Universitario Doctor Negrín (Las Palmas de Gran Canaria, Spain) and subsequently by the local Ethics Committees of all the participating centres. This study was carried out in compliance with the Declaration of Helsinki.

Major CNS NP-SLE manifestations

The major CNS NP-SLE manifestations analysed in this study were (a) cerebrovascular disease (CVD) and (b) transverse myelitis according to the Systemic Lupus International Collaborating Clinics (SLICC)/ACR-damage index (SDI) definition [14]; (c) seizures, (d) psychosis and (e) organic brain syndrome, in accordance with the SELENA-SLEDAI (Safety

of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index) definition [15]. Other previously described major CNS NP-SLE manifestations such as major cognitive dysfunction, movement disorder, aseptic meningitis and demyelinating syndrome were not included in this study since they were anecdotally reported ($n < 5$) or not specifically recorded in RELESSER. Furthermore, major CNS NP-SLE manifestations were classified based on the underlying pathophysiology into focal and diffuse NP-SLE according to the 1999 ACR case definitions [4]. Focal NP-SLE is the result of vasculopathy or thromboembolic events and included CVD, seizure and transverse myelitis. On the other hand, diffuse NP-SLE is related to autoimmune-inflammatory processes and included psychosis and organic brain syndrome. All major CNS NP-SLE manifestations were attributed to SLE based on clinical judgement. These manifestations were considered to be related to SLE when they were directly related to disease activity and after the exclusion of other aetiologies explaining these symptoms (primary NP etiology, infections, comorbidities, drug toxicity).

Clinical and laboratory data

Clinical data included the following variables: 1) sociodemographic variables including age at inclusion and age at SLE diagnosis, gender, race and SLE duration in years categorized into <1 year, 1 to ≤10 years and >10 years, 2) SLE clinical manifestations as presented in Table 1 and the presence ever of antiphospholipid syndrome (APS) according to the Sydney classification criteria for definite APS [16], 3) irreversible damage was calculated with the SDI, excluding the NP manifestations for a better assessment of the effect of disease damage [14,17], 4) presence ever of comorbidities including cancer, severe infections as previously defined by our group [18], traditional risk factors contributing to cardiovascular disease (smoking status, diabetes mellitus and hypertension) and other chronic diseases (chronic obstructive pulmonary disease, ischemic heart disease, heart failure, rhythm disorders and end stage renal disease), 5) use of glucocorticoids, antimalarials and other immunosuppressive therapies during the course of the disease and 6) single primary cause of death from a set of predefined categories including SLE-related causes specifying involvement, infections, vascular disease (including non-SLE related cardiovascular and cerebrovascular origin), cancer and other causes. Laboratory data included the following: 1) presence ever of SLE-related antibodies: anti-dsDNA, anti-Sm, anti-RNP, anti-SSA/Ro, anti-SSB/La, and antiphospholipid antibodies (aPL) including anticardiolipin IgG and IgM, anti-Beta2 glycoprotein 1 antibody IgG and IgM and lupus anticoagulant, and 2) presence of hypocomplementemia defined as ever low C3 or C4 levels.

Statistical analysis

Demographic, clinical and laboratory parameters were described as proportions, as mean and standard deviations (SD) or as median and interquartile range (IQR), as appropriate. Prevalence was the number of individuals satisfying the individual major CNS NP-SLE definitions divided by the total number of patients with SLE included in the analysis. Baseline characteristics were compared between groups using the X^2 test, the Student t-test (Fisher exact test when necessary), or the Mann–Whitney U test. Age- and gender-adjusted prevalence and incidence rates of major CNS NP-SLE and any of the individual major CNS NP-SLE manifestations per 1000 person-years (py) were calculated. These were additionally stratified by time since SLE diagnosis (cut-off values for SLE duration; <1, 1 to ≤10, >10 years). The confidence intervals were calculated using Poisson distribution. The number of SLE patients developing major CNS NP-SLE or any of its individual manifestations who died during follow-up was analysed with Kaplan-Meier survival curves. The annual mortality rate as well as the time to 10%, 25% and 50% mortality was analysed for major CNS NP-SLE manifestations as a group, individually and clustered into focal or diffuse NP-

Table 1
Clinical, serological and treatment characteristics of the 3591 included patients with SLE and variables associated with the development of major CNS NP-SLE.

	N (%) or mean (SD) or median (IQR) Total	N (%) or mean (SD) or median (IQR) Major CNS NP-SLE	N (%) or mean (SD) or median (IQR)	*P* value
		Yes ($N = 412$)	No ($N = 3179$)	
Female	3242 (90%)	363 (88%)	2879 (91%)	0.128
Race/ethnicity				0.171
Caucasian	3254 (91%)	375 (91%)	2879 (91%)	
Hispanic	181 (5%)	22 (5%)	159 (5%)	
Other	55 (2%)	2 (<1%)	53 (2%)	
Age at diagnosis SLE, years	35.2 (14.7)	34.5 (16.3)	35.2 (14.4)	0.382
Duration SLE at inclusion, years	11.6 (8.5)	13.6 (8.9)	11.3 (8.4)	
0 - < 1 year	275 (8%)	23 (6%)	252 (8%)	
1 - < 10 years	1509 (42%)	142 (34%)	1367 (43%)	
> 10 years	1807 (50%)	247 (60%)	1560 (49%)	
Clinical manifestations (ever)				
Cutaneous involvement	2941 (82%)	332 (81%)	2609 (82%)	0.523
Arthritis	2764 (77%)	297 (72%)	2467 (78%)	0.004
Nephritis	1066 (30%)	182 (44%)	884 (28%)	<0.001
Hemolytic anemia	308 (9%)	51 (12%)	257 (8%)	0.006
Thrombopenia	801 (22%)	136 (33%)	665 (21%)	<0.001
Vasculitis	311 (9%)	72 (17%)	239 (8%)	<0.001
Pericarditis	562 (16%)	110 (27%)	452 (14%)	<0.001
Myocarditis	24 (<1%)	9 (2%)	15 (<1%)	<0.001
Liebman-Sacks endocarditis	34 (<1%)	20 (5%)	14 (<1%)	<0.001
Pulmonary manifestations	200 (6%)	34 (8%)	166 (5%)	0.016
Gastrointestinal manifestations	129 (4%)	19 (5%)	110 (3%)	0.204
Diagnosis APS	490 (14%)	144 (35%)	346 (11%)	<0.001
Traditional risk factors and other comorbidities (ever)				
Hypertension	1034 (29%)	181 (44%)	853 (27%)	<0.001
Diabetes mellitus	144 (4%)	29 (7%)	115 (4%)	0.003
Smoking	1325 (37%)	158 (38%)	1167 (37%)	0.696
Chronic obstructive pulmonary disease	96 (3%)	13 (3%)	83 (3%)	0.517
Pulmonary thromboembolism	101 (3%)	22 (5%)	79 (3%)	0.007
Ischemic heart disease	119 (4%)	20 (5%)	99 (3%)	0.005
Heart failure	150 (5%)	26 (6%)	124 (4%)	<0.001
Rhythm disorders	129 (4%)	18 (4%)	111 (4%)	0.348
ESRD	93 (3%)	13 (3%)	80 (3%)	0.408
SDI	2 (1–3)	3 (2–4)	2 (1–3)	<0.001
Antibodies and complement (ever)				
Anti-dsDNA*	2568 (73%)	326 (81%)	2242 (72%)	<0.001
Anti-Sm†	723 (21%)	92 (23%)	631 (21%)	0.327
Anti-Ro*	1374 (40%)	147 (37%)	1227 (40%)	0.212
Anti-La*	675 (19%)	61 (15%)	614 (20%)	0.026
Anti-RNP*	868 (25%)	106 (26%)	762 (25%)	0.583
Anticardiolipin IgG†	815 (25%)	162 (41%)	653 (23%)	<0.001
Anticardiolipin IgM†	660 (20%)	113 (29%)	547 (19%)	<0.001
Anti-Beta-2 glycoprotein 1 IgG‡	287 (13%)	60 (25%)	227 (12%)	<0.001

(*continued on next page*)

Table 1 (*continued*)

	N (%) or mean (SD) or median (IQR) Total	N (%) or mean (SD) or median (IQR) Major CNS NP-SLE		*P* value
		Yes ($N = 412$)	No ($N = 3179$)	
Anti-Beta-2 glycoprotein 1 IgM‡	296 (14%)	52 (22%)	244 (13%)	<0.001
LAC‡	619 (24%)	129 (40%)	490 (22%)	<0.001
Low complement*	2736 (78%)	341 (85%)	2395 (77%)	<0.001
Treatment (ever)				
Glucocorticoids*	3034 (89%)	377 (94%)	2657 (88%)	<0.001
Antimalarials*	2832 (83%)	298 (76%)	2534 (84%)	<0.001
Methotrexate*	567 (17%)	55 (14%)	512 (17%)	0.1314
Azathioprine*	1116 (33%)	192 (49%)	924 (31%)	<0.001
Mycophenolate*	515 (15%)	88 (22%)	427 (14%)	<0.001
Cyclophosphamide*	758 (22%)	173 (44%)	585 (20%)	<0.001
Rituximab*	220 (6%)	43 (11%)	177 (6%)	<0.001

APS: antiphospholipid syndrome; ESRD: end stage renal disease; LAC: lupus anticoagulant; SDI: SLICC (Systemic Lupus Erythematosus International Collaborating Clinics) damage index; SLE: systemic lupus erythematosus.

* Missing data in < 5%.

† Missing data in < 10%.

‡ Missing data in > 20%.

SLE. Furthermore, Kaplan-Meier survival curves (e.g. patients with and without a specific NP-SLE manifestation) were compared using the log-rank test. The independent contribution of the presence of major CNS NP-SLE or any of its manifestations during follow-up to mortality was analysed in a multivariable Cox regression model. To calculate the hazard ratios (HR) and 95% confidence intervals (CI) we started with a clinical model predicting mortality including the following potentially explanatory variables: age at SLE onset, presence during the course of the disease of severe infection, lupus nephritis or respiratory manifestations, APS, cancer and factors contributing to cardiovascular disease (smoking status, diabetes mellitus and hypertension). Thereafter, in order to evaluate their independent explanatory effect on mortality, major CNS NP-SLE as a composite endpoint and the individual major CNS NP-SLE manifestations (altogether, one by one and grouped into focal and diffuse; this in separate models) were added to the model. The proportional hazards assumption for the Cox regression analyses was fulfilled in all cases. The causes of death of patients ever found to have major CNS NP-SLE in the course of the disease were described. A p-value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, N.Y., USA).

Results

Prevalence and incidence rates

A total of 3591 SLE patients were included in the analysis. The mean age (Standard deviation [SD]) of all patients at the time of SLE diagnosis was 35.2 years (SD 14.7), 90% were female and 91% Caucasians. The mean duration of SLE was 11.6 years (SD 8.5). Table 1 shows a broad array of variables and its associations with the development of major CNS NP-SLE. In general, patients with major CNS NP-SLE had a more severe disease, more damage, a higher prevalence of hypertension and APS, and they received more glucocorticoids and immunosuppressive therapies in the course of disease. The mean duration of follow-up was 11.3 (SD 7.7) years. The total number of person-years of follow-up was 41,544. A total of 412 (11%) patients presented at least one major CNS NP-SLE manifestation. These patients presented a total of 522 major CNS NP-SLE manifestations. A total of 323 (9%) patients presented one major CNS NP-SLE manifestation. Furthermore 70 (2%) patients presented two, 17 (0.5%) patients presented three and 2 (<0.1%) patients presented four major CNS NP-SLE manifestations. Prevalence and incidence rates are shown in Table 2. The most frequent major CNS NP-SLE manifestations were CVD with 201 (6%) patients and seizures with 154 (4%) patients. A total of 85 (2%) patients presented organic brain syndrome, 57 (<2%) psychosis and 25 (<1%) transverse myelitis. The mean age at diagnosis of major CNS NP-SLE was 50.9 years (SD 17.2). The mean disease duration until the presentation of the first major CNS NP-SLE manifestation was 7.3 years (SD 3.7). The incidence rate of any major CNS NP-SLE was 10.92 per 1000 py (95%CI 9.89–12.03). The incidence rate was 261.65 per 1000 py (95%CI 165.86–392.6) during the first year since SLE diagnosis, decreasing to 17.86 per 1000 py (95% CI 15.05–21.05) in patients with 1–10 years history of SLE, and to 8.32 per 1000 py (95%CI 7.31–9.42) for patients with a history of SLE >10 years. The same gradient was also found for the individual major CNS NP-SLE manifestations (Table 2).

Mortality of patients with major CNS NP-SLE

A total of 199 out of 3591 patients with SLE died. Among the patients with ever major CNS NP-SLE, a total of 61 out of 412 patients died. In patients with major CNS NP-SLE the annual mortality rate was 10.8%

Table 2
Prevalence, person-years and incidence rates for major CNS NP-SLE (individual manifestations and grouped).

	N (%)	Person-years	Incidence Rate (95% CI)[a]
SLE without NP	3179 (88.5)		
Major CNS NP-SLE	412 (11.5)	37,728.5	10.92 (9.89 - 12.03)
0 - < 1 year [b]	23/275 (8.4)	87.9	261.65 (165.86 - 392.60)
1 - ≤ 10 years	142/1509 (9.4)	7949.7	17.86 (15.05 - 21.05)
> 10 years	247/1807 (13.7) **	29,690.9	8.32 (7.31 - 9.42)
Cerebrovascular disease	201 (5.6)	40,154.1	5.01 (4.34 - 5.75)
0 - < 1 year	10/275 (3.6)	92.2	108.50 (52.03 - 199.54)
1 - ≤ 10 years	75/1509 (5.0)	8228.5	9.11 (7.17 - 11.43)
> 10 years	116/1807 (6.4)	31,833.5	3.64 (3.01 - 4.37)
Psychosis	57 (1.6)	40,935.4	1.39 (1.05 - 1.80)
0 - < 1 year	5/275 (1.8)	95.0	52.64 (17.09 - 122.84)
1 - ≤ 10 years	19/1509 (1.3)	8422.7	2.26 (1.36 - 3.52)
> 10 years	33/1807 (1.8) **	32,417.7	1.02 (0.70 - 1.43)
Seizure	154 (4.3)	39,837.5	3.87 (3.28 - 4.53)
0 - < 1 year	11/275 (4.0)	94.1	116.85 (58.33 - 209.07)
1 - ≤ 10 years	48/1509 (3.2)	8287.7	5.79 (4.27 - 7.68)
> 10 years	95/1807 (5.3) **	31,455.7	3.02 (2.44 - 3.69)
Transverse myelitis	25 (0.7)	41,323.1	0.60 (0.39 - 0.89)
0 - < 1 year	0/275 (0)	97.5	0
1 - ≤ 10 years	6/1509 (0.4)	8484.3	0.71 (0.26 - 1.54)
> 10 years	19/1807 (1.1)	32,741.2	0.58 (0.35 - 0.91)
Organic brain syndrome	85 (2.4)	40,530.9	2.10 (1.68 - 2.59)
0 - < 1 year	3/275 (1.1)	96.6	31.04 (6.40 - 90.72)
1 - ≤ 10 years	26/1509 (1.7)	8430.5	3.08 (2.01 - 4.52)
> 10 years	56/1807 (3.1) **	32,003.7	1.75 (1.32 - 2.27)

a. Incidence rates per 1000 person-years, adjusted for age and gender. The confidence intervals were calculated using Poisson distribution.

b. Data stratified according to duration of SLE in years at the time of major CNS NP-SLE manifestations (<1 year, 1 - ≤10 years and >10 years).

* $p<0.05$; ** $p<0.01$.

CNS: central nervous system; NP: neuropsychiatric; SLE: systemic lupus erythematosus.

compared to the 3.8% in patients with SLE without ever NP-SLE. Table 3 shows the annual mortality rates of other individual major CNS NP-SLE manifestations. CVD (14%) and organic brain syndrome (15.5%) showed the highest annual mortality rates among the individual major CNS NP-SLE manifestations. The 10% mortality rate was reached after 22.8 years in the group of SLE patients without ever NP-SLE and after 12.3 years in the group of patients with major CNS NP-SLE. Among the individual major CNS NP-SLE manifestations, the 10% mortality rate was reached markedly earlier in patients with CVD (9.8 years) and organic brain syndrome (7.1 years). Similar results were found for the 25% mortality rate (Table 3). Kaplan-Meier cumulative survival rates for major CNS NP-SLE and for the individual major CNS NP-SLE manifestations are shown in Fig. 1. When analysing major CNS NP-SLE as a group, mortality was higher in patients with compared to patients without ever major CNS NP-SLE manifestations (HR 2.59; 95% CI 1.91–3.52). Similar results were found for mortality in patients with CVD compared to patients without CVD (HR 3.3; 95% CI 2.29–4.75), seizure (HR 2.51; 95% CI 1.61–3.91), organic brain syndrome (HR 3.15; 95% CI 1.92–5.17) and transverse myelitis (HR 3.52; 95% CI 1.44–8.60) but not for psychosis (HR 1.71; 95% CI 0.76–3.89; $P = 0.19$). Mortality of patients with focal (HR 2.87; 95% CI 2.09–3.94) and diffuse (HR 2.62; 95% CI 1.64–4.20) NP-SLE manifestations was also significantly higher compared to that of patients without major CNS NP-SLE.

Compared to patients without major CNS NP-SLE, patients with major CNS NP-SLE had a 2-fold higher risk for mortality, adjusted for other relevant clinical variables (HR 1.85, 1.29–2.67). When modeling the individual NP-SLE manifestations, CVD (HR 2.17, 1.41–3.33) and organic brain syndrome (HR 2.11, 1.19–3.74) accounted as independent prognostic factors for poor survival, also adjusted for potential confounders (Table 4). When all individual NP-SLE manifestations were modelled together, CVD (HR 1.99, 1.27–3.12) was the one significantly associated with mortality. When categorizing NP-SLE into focal and diffuse, the presence of both focal NP-SLE (HR 1.93, 1.32–2.82) and diffuse NP-SLE (HR 1.83, 1.06–3.16) during the course of the disease were also predictors of mortality in patients with SLE.

Causes of death of patients with major CNS NP-SLE

SLE-related causes accounted for the most common cause of death of NP-SLE patients (34%). Among all the SLE-related causes of death of patients with ever major CNS NP-SLE, CNS involvement was the leading cause. A total of 7 patients (out of 3591 SLE patients (0.2%), out of 412 patients with major CNS NP-SLE patients (<2%)) died because of causes directly attributed to CNS involvement. Of the seven deaths among the NP-SLE patients, four were due to CVD, two due to seizure and one due to organic brain syndrome. Six out of these seven patients were already known with major CNS NP-SLE; a total of 9 major CNS NP-SLE manifestations had been recorded in the clinical history before they died (4 CVD, 2 seizure, 1 organic brain syndrome, 1 psychosis, 1 transverse myelitis). Forty out of 61 (66%) patients with ever major CNS NP-SLE died because of non-SLE related causes. Vascular disease was the leading cause in 20 patients (33%); among them non-SLE-related cerebrovascular accident accounted for 55% (11 patients) and cardiovascular disease for 40% (8 patients) of the cases. In patients without ever major CNS NP-SLE significantly less patients died due to vascular disease (25%; $p<0.05$); cardiovascular disease accounted for 70% and cerebrovascular accident for 13% of the cases. All data are shown in Table 5.

Discussion

The RELESSER registry has provided the basis to investigate several SLE aspects in Southern European Caucasian patients, covering from specific SLE manifestations like lupus nephritis to cumulative organ damage [19,20]. The present study provides further evidence that major CNS NP-SLE and its individual NP manifestations, though uncommon, occur more often in the first year after SLE diagnosis and decrease in the course of the disease. Our results are in line with previous data reported from other cohorts worldwide and emphasize that awareness is required in the very early phases of SLE since timely recognition of these manifestations has important implications for the subsequent disease course [21,22].

Our survival analysis shows that patients developing major CNS NP-SLE in the course of the disease have poorer survival than those who never developed these manifestations, more specifically with a mortality two times higher. Previous studies analysing the contribution of NP-SLE as composite endpoint on SLE survival found inconsistent results. Some retrospective reports suggested that major NP-SLE or NP-damage were not independent contributors to mortality in SLE [23–25]. The multi-ethnic LUMINA (Lupus in Minorities: Nature vs Nurture) cohort also found that only overall damage and not individual NP-damage contributed to mortality [26]. On the other hand, recent studies on larger prospective SLE cohorts found different results. A single-center study on Asian patients found that the presence of NP-SLE (HR 3.09, CI 1.03–9.21), and especially focal CNS NP-SLE (HR 7.83, CI 2.12–28.96), increases the risk of mortality in patients with SLE [27]. Recently, a 10-year follow-up analysis on the prospective SLICC inception cohort also demonstrated that patients presenting with NP manifestations attributed to SLE had a higher mortality (16%) than patients without NP-SLE (6%) or patients with NP manifestations non-related to SLE (7%) [28]. Our results, although using a retrospective study design, are consistent with these prospective studies and underscore the contribution to mortality of major CNS NP-SLE. Furthermore we show that not only focal NP-SLE but also diffuse NP-SLE may contribute to mortality in SLE.

Another important finding of our study is that the presentation of the individual major CNS NP-SLE manifestations may differently affect survival of SLE patients. We demonstrate that CVD and organic brain syndrome independently contribute to mortality in SLE even when examined in conjunction with other variables known to explain mortality. Both CVD and organic brain syndrome are known to be among the most severe NP manifestations in SLE and have been previously related to lower survival [29–31]. CVD related to SLE mainly occurs in the early

Table 3
Number of deaths, annual mortality rate and time to death in patients with major CNS NP-SLE.

	Number of deaths (%) [a]	Annual mortality rate (CI 95%)	10% mortality time (years)	25% mortality time (years)	50% mortality time (years)
SLE without NP	138/3179 (4%)	3.8% (3.2% to 4.5%)	22.8	35.2	–
Major CNS NP-SLE	61/412 (15%)	10.8% (8.3% to 13.9%)	12.3	24.8	35.2
Cerebrovascular disease	38/201 (19%)	14% (9.9% to 19.2%)	9.8	23.6	30.9
Psychosis	6/57 (11%)	7.4% (2.7% to16.2%)	18.4	–	–
Seizure	23/154 (15%)	10.4% (6.6% to 15.6%)	15.2	26.4	30.9
Transverse Myelitis	5/25 (20%)	13.7% (4.5% to 32%)	15.2	24.8	29.6
Organic brain syndrome	18/85 (21%)	15.5% (9.2% to 24.4%)	7.1	23.1	30.9
Focal NP-SLE	54/343 (16%)	11.6% (8.7% to 15.1%)	9.9	24.8	30.9
Diffuse NP-SLE	20/115 (17%)	11.5% (7.1% to 17.7%)	9.8	23.1	–

a. More than one major CNS NP-SLE per patient and presence of both focal and diffuse NP-SLE in the same patient possible.
CNS: central nervous system; NP: neuropsychiatric; SLE: systemic lupus erythematosus.

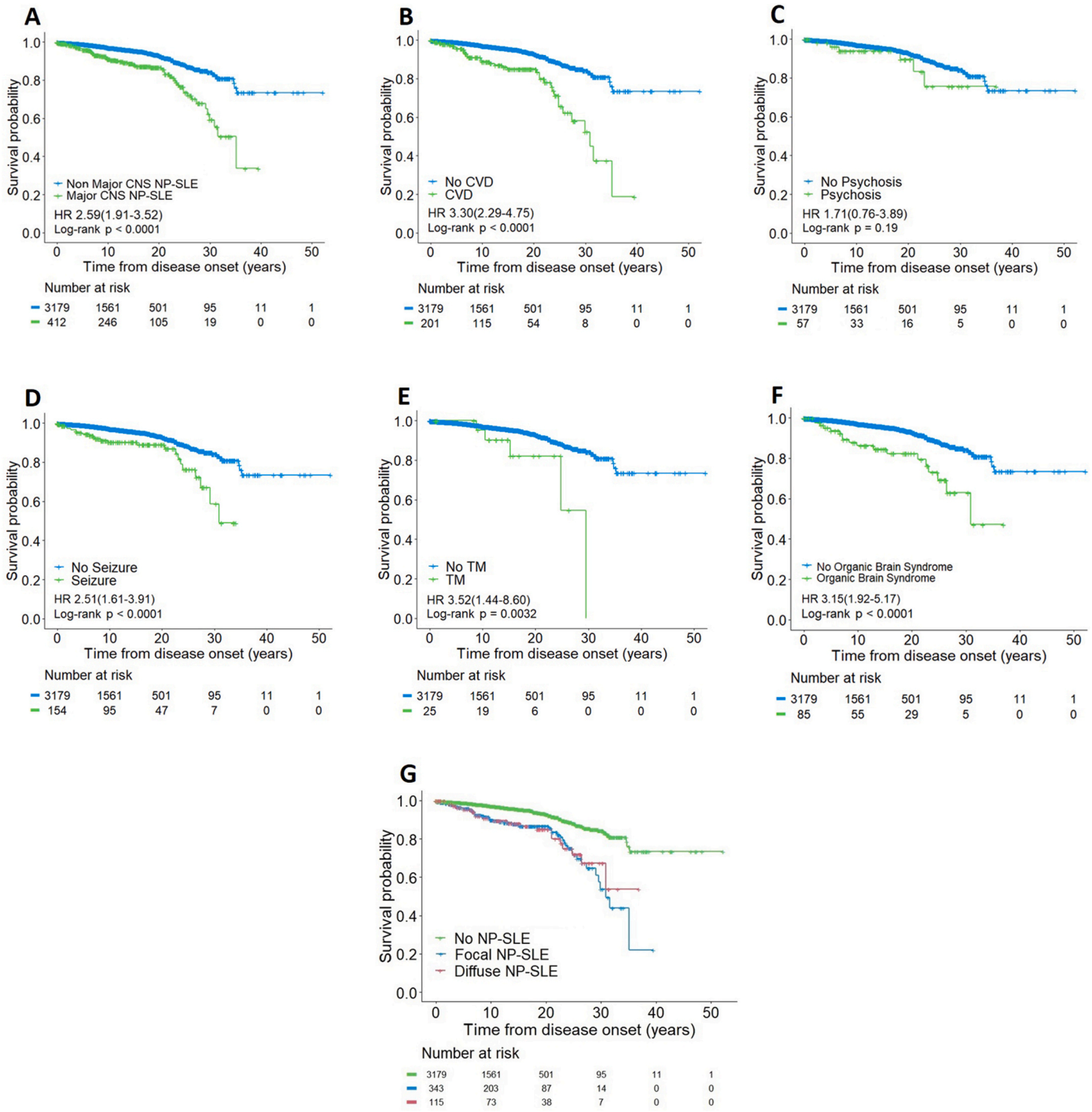

Fig. 1. Survival analysis (Kaplan–Meier graphs) for patients with major CNS NP-SLE in the RELESSER-TRANS cohort. Mortality is plotted according to the presentation or absence of major CNS NP-SLE (A) and individual major CNS NP-SLE manifestations (B-F); cerebrovascular disease (CVD) (B), psychosis (C), seizure (D), transverse myelitis (TM) (E) organic brain syndrome (F) and focal and diffuse NP-SLE (G).

stages of the disease and is thought to be the consequence of endothelial activation due to systemic inflammation or a prothrombotic state due to the presence of aPL [32,33]. In contrast, brain dysfunction due to an autoimmune or inflammatory process driven by antibodies is frequently proposed as the underlying mechanism in the pathogenesis of organic brain syndrome [34]. Although they may not share the same underlying pathophysiologic mechanism, both CVD and organic brain syndrome probably exert their influence through damage. Not all the NP manifestations affected survival in our cohort. The impact of seizure on survival of SLE patients has been previously reported. This manifestation was found to be a predictor for other serious clinical events and therefore to be an important contributor to the accrual of damage in SLE [35]. In our study, we also found that seizure had poorer survival rates but this NP manifestation was not independently associated to mortality. Our results also show that lupus psychosis has a better prognosis than those major CNS NP-SLE manifestations leading to damage. Hanly et al. have previously analysed the long-term physician and patient reported outcomes of patients with lupus psychosis on the SLICC cohort, finding substantially good outcomes over time following adequate treatment for these patients [36].

Table 4
Major CNS NP-SLE manifestations as predictors of mortality in the RELESSER-TRANS cohort.

	Model 1 Hazard ratio (CI 95%)	Model 2 Hazard ratio (CI 95%)	Model 3 Hazard ratio (CI 95%)	Model 4 Hazard ratio (CI 95%)	Model 5 Hazard ratio (CI 95%)	Model 6 Hazard ratio (CI 95%)	Model 7 Hazard ratio (CI 95%)	Model 8 Hazard ratio (CI 95%)	Model 9 Hazard ratio (CI 95%)
Severe infection	2.09 (1.48–2.96) ***	2.01 (1.41–2.86) ***	2.06 (1.45–2.92) ***	2.24 (1.59–3.16) ***	2.24 (1.59–3.17) ***	2.22 (1.57–3.13) ***	2.27 (1.61–3.2) ***	2.1 (1.49–2.98) ***	2.21 (1.56–3.12) ***
Nephritis	1.75 (1.16–2.66) **	1.82 (1.2–2.76)**	1.8 (1.19–2.73)**	1.74 (1.15–2.64) **	1.7 (1.12–2.57)*	1.7 (1.12–2.58)*	1.7 (1.12–2.57)*	1.82 (1.2–2.76)**	1.7 (1.12–2.58)*
Respiratory manifestations	1.54 (1.06–2.24)*	1.57 (1.08–2.29)*	1.62 (1.12–2.36)*	1.54 (1.06–2.24)*	1.54 (1.06–2.23)*	1.51 (1.04–2.2)*	1.55 (1.07–2.25)*	1.59 (1.1–2.31)*	1.5 (1.03–2.19)*
Cancer	1.42 (0.93–2.17)	1.46 (0.95–2.24)	1.41 (0.93–2.16)	1.37 (0.89–2.09)	1.34 (0.88–2.05)	1.4 (0.91–2.14)	1.33 (0.87–2.04)	1.42 (0.93–2.16)	1.39 (0.91–2.12)
Age of disease onset	1.06 (1.05–1.08) ***	1.07 (1.05–1.08) ***	1.06 (1.05–1.08) ***	1.06 (1.05–1.08) ***	1.06 (1.05–1.08) ***	1.06 (1.05–1.08) ***	1.06 (1.05–1.08) ***	1.06 (1.05–1.08) ***	1.06 (1.05–1.08) ***
APS	1.45 (0.99–2.1)	1.34 (0.91–1.99)	1.38 (0.94–2.03)	1.54 (1.06–2.23)*	1.6 (1.1–2.32)*	1.55 (1.06–2.25)*	1.61 (1.11–2.33)*	1.43 (0.98–2.08)	1.55 (1.07–2.26)*
Hypertension ever	0.77 (0.54–1.1)	0.74 (0.51–1.05)	0.75 (0.53–1.08)	0.76 (0.53–1.09)	0.78 (0.55–1.11)	0.75 (0.52–1.07)	0.78 (0.55–1.11)	0.76 (0.54–1.09)	0.76 (0.53–1.09)
Smoking ever	1.12 (0.8–1.57)	1.09 (0.77–1.54)	1.08 (0.76–1.51)	1.16 (0.83–1.63)	1.18 (0.84–1.65)	1.16 (0.83–1.62)	1.17 (0.83–1.64)	1.11 (0.79–1.55)	1.17 (0.83–1.64)
Diabetes mellitus ever	1.31 (0.84–2.06)	1.27(0.8–2)	1.31 (0.83–2.06)	1.32 (0.84–2.06)	1.27 (0.81–2.01)	1.3 (0.83–2.05)	1.31 (0.83–2.06)	1.34 (0.85–2.1)	1.26 (0.8–1.98)
Glucocorticoids ever	2.42 (0.88–6.66)	2.43 (0.88–6.71)	2.47 (0.89–6.82)	2.49 (0.9–6.88)	2.47 (0.89–6.81)	2.43 (0.88–6.7)	2.48 (0.9–6.84)	2.42 (0.88–6.69)	2.42 (0.88–6.69)
Antimalarials ever	0.43 (0.31–0.6) ***	0.42 (0.3–0.58) ***	0.42 (0.3–0.59)***	0.43 (0.3–0.6)***	0.42 (0.3–0.59) ***	0.41 (0.3–0.58)***	0.42 (0.3–0.59) ***	0.43 (0.31–0.61) ***	0.42 (0.3–0.59)***
Major CNS NP-SLE	1.85 (1.29–2.67) ***								
Cerebrovascular disease		1.99 (1.27–3.12) **	2.17 (1.41–3.33) ***						
Seizure		1.12 (0.61–2.06)		1.57 (0.93–2.66)					
Psychosis		1.58 (0.62–3.99)			1.73 (0.69–4.33)				
Organic brain syndrome		1.6 (0.83–3.1)				2.11 (1.19–3.74) *			
Transverse myelitis		1.03 (0.14–7.47)					1.22 (0.17–8.84)		
Focal NP-SLE								1.93 (1.32–2.82) ***	
Diffuse NP-SLE									1.83 (1.06–3.16) *

*$P<0.05$; ** $P<0.01$; *** $P<0.001$.
APS: antiphospholipid syndrome; CNS: central nervous system; NP: neuropsychiatric; RELESSER-TRANS: Registry of Systemic Lupus Erythematosus Patients of the Spanish Society of Rheumatology (SER); SLE: systemic lupus erythematosus.

Although major CNS NP-SLE carries a higher mortality risk overtime in SLE, the current study shows that these manifestations may be an uncommon direct cause of death in SLE patients. The cause of death was slightly different between patients with and without ever major CNS NP-SLE. Patients with major CNS NP-SLE died slightly more of SLE-related causes and of vascular disease, especially cerebrovascular accident due to other causes than lupus. Cerebrovascular accident non-related to SLE tends to occur at late stages of the disease course and is mainly caused by atherosclerosis due to traditional cardiovascular risk factors such as hypertension, hyperlipidaemia, smoking and diabetes mellitus, all of them common comorbidities in SLE [37]. Our study might, to a certain degree, reinforce the results found in other studies showing that established damage, in this case NP-damage, predicts more damage accrual and subsequently more mortality [38,39]. There may be two important points explaining the higher mortality of these patients. First, patients with SLE developing NP-damage have more severe disease. A higher SLE disease activity and major organ involvement lead to higher damage scores also in other organs (e.g. lupus nephritis) and subsequently to more comorbidities and more therapy related complications [33,35,40]. Second, the presence of aPL has been linked to NP-SLE but also to greater damage accruals and mortality in our cohort [41]. However, in our study, CVD was identified as a predictor of mortality independently of the effect of other severe SLE involvement such as lupus nephritis and the presence of APS, which were also accounted for in the models. Furthermore, the same findings were found after the inclusion of comorbidities and the use of glucocorticoids in the model.

The presence of the higher mortality risk over time seems contradictory with the previously reported positive short-term outcomes of NP-SLE manifestations. Previous studies have shown that NP-SLE manifestations are more likely to resolve than NP manifestations not related to SLE [42] Good clinical outcomes with restoring of the radiology and a meaningful improvement of the quality of life have been described in NP-SLE after receiving immunosuppressive therapy, especially in those NP manifestations caused by an underlying inflammatory pathophysiological process [6,43]. It remains a matter of further research if timely intensive immunosuppressive treatment and early and complete reversibility of these severe NP manifestations may avoid or diminish irreversible NP-damage subsequently leading to a lower mortality.

Table 5
Causes of mortality in patients with and without major CNS NP-SLE.

	Major CNS NP-SLE $n = 61$ N (%)	SLE without major CNS NP-SLE $n = 118$[†] N (%)
SLE	**21 (34%)**[*]	**26 (22%)**
Renal	3 (14%)	3 (12%)
Major CNS NP-SLE	7 (33%)	0 (0%)
Cardiovascular	2 (10%)	2 (8%)
Respiratory	5 (24%)	16 (62%)
Gastrointestinal	2 (10%)	4 (15%)
Hematological	1 (5%)	0 (0%)
Others	1 (5%)	1 (4%)
Infection	**13 (21%)**	**33 (28%)**
Bacteremia/Sepsis	6 (46%)	15 (45%)
Respiratory	2 (15%)	12 (36%)
Urinary	2 (15%)	1 (3%)
Endocarditis	2 (15%)	2 (6%)
CNS	0 (0%)	1 (3%)
Gastrointestinal	0 (0%)	2 (6%)
Other	1 (8%)	0 (0%)
Vascular disease	**20 (33%)**[*]	**30 (25%)**
Cardiovascular	8 (40%)	21 (70%)
CVA non-related to SLE	11 (55%)	4 (13%)
Thromboembolic	0 (0%)	2 (7%)
Other	1 (5%)	3 (10%)
Cancer	**4 (7%)**	**27 (23%)**
Hematological	2 (50%)	3 (11%)
Other	2 (50%)	24 (89%)
Other	**3 (5%)**	**2 (2%)**

CNS: central nervous system; CVA: cerebrovascular accident; NP: neuropsychiatric; SLE: systemic lupus erythematosus.
[*] $P<0.05$.
[†] In 20 out of 3179 SLE patients without major CNS NP-SLE was the cause of mortality unknown.

Our study has several strengths. This is the largest cohort in Europe providing a detailed assessment of major CNS manifestations in SLE patients. The large enrolment represents a very useful opportunity to analyze a representative number of subjects developing individual major CNS NP-SLE manifestations and not only NP-SLE as a composite endpoint. Some limitations inherent to the study design should be taken into account. Firstly, the RELESSER was not designed to specifically evaluate the major CNS NP-SLE manifestations in SLE patients. Due to the same reason we could not include other NP-SLE manifestations such as major cognitive dysfunction. This could have led to an under or overestimation of the frequency of some of the individual major CNS NP-SLE manifestations. Second, we have used definitions included in two different indexes to describe the individual major CNS NP-SLE manifestations. The use of the 1999 ACR nomenclature to define all of them would have been more appropriate [4]. Third, the unavailability of dates of presentation of some comorbidities and use of several medications limited our ability to assess related factors of major CNS NP-SLE manifestations and to apply any of the algorithms used for the attribution of NP events in SLE [44,45].

In summary, major CNS NP-SLE is uncommon and mostly presents in the first years of SLE course. The presentation of major CNS NP-SLE manifestations leads to an important disease burden and less survival in SLE patients. Among the individual major CNS NPS-SLE manifestations, in our cohort, CVD and organic brain syndrome contributed as predictors of mortality. Our study emphasizes how preventing NP-damage may have important long-term prognostic implications in SLE patients. Early recognition and treatment of major CNS NP-SLE manifestations but also strict control of SLE activity and comorbidities during the posterior course of disease may help achieving better outcomes for these patients.

Declaration of Competing Interest

None declared.

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