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Psychosis in Systemic Lupus Erythematosus

Results from an international, inception cohort study

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Objectives: To determine, in a multi-ethnic/racial, prospective SLE inception cohort, the frequency, attribution, clinical and autoantibody associations with lupus psychosis and the short and long-term outcome as assessed by physicians and patients.

Methods: Patients were evaluated annually for 19 neuropsychiatric (NP) events including psychosis. SLE disease activity 2000, SLICC/ACR damage index and SF-36 scores were collected. Time to event and linear regressions were used as appropriate.

Results: Of 1,826 SLE patients, 88.8% were female, 48.8% Caucasian. The mean±SD age was 35.1±13.3 years, disease duration 5.6±4.2 months and follow-up 7.4±4.5 years. There were 31 psychotic events in 28/1,826 (1.53%) patients and most [(26/28; 93%)] had a single event. In the majority of patients [20/25; (80%)] and events [28/31; (90%)] psychosis was attributed to SLE, usually within 3 years of SLE diagnosis. Positive associations [hazard ratio and 95% confidence interval [HR (95%CI)] with lupus psychosis were prior SLE NP events [3.59, (1.16, 11.14)], male sex [3.0, (1.20, 7.50)], younger age at SLE diagnosis [(per 10 years younger), 1.45 (1.01, 2.07)] and African ancestry [4.59 (1.79, 11.76)]. By physician assessment most psychotic events resolved by the second annual visit following onset, in parallel with an improvement in patient reported SF-36 summary and subscale scores.

Conclusion: Psychosis is an infrequent manifestation of NPSLE. Generally, it occurs early after SLE onset and has a significant negative impact on health status. As determined by patient and physician report, the short and long term outlook is good for most patients, though careful follow-up is required.

Neuropsychiatric (NP) events are one of the features of systemic lupus erythematosus (SLE) but their frequency and attribution to SLE or other causes is variable. Overall, approximately one third are caused directly by SLE (1), but for individual manifestations this varies between 0% and 100% (2, 3). The outcome for individual NPSLE manifestations, especially rare NP events, is derived from observational cohorts of well characterized patients followed over prolonged periods.

One of the rarer NP events is lupus psychosis which is part of both the ACR (4) and SLICC (5) classification criteria for SLE. Characterized by delusions and hallucinations, it is a dramatic presentation of NPSLE (6, 7). It is one of the few manifestations of nervous system disease in SLE associated, albeit inconsistently, with a lupus specific autoantibody against ribosomal P (8-10). The infrequent occurrence of psychosis has limited the number of clinical studies and most consist of case series obtained by review of medical records.

In the present study of lupus psychosis, we determined its frequency, attribution, clinical and autoantibody associations and the outcome assessed by physicians and patients in a large, multi-ethnic/racial, prospective, inception cohort of SLE patients.

Patients and Methods

Research study network: The study was conducted by the Systemic Lupus International Collaborating Clinics (SLICC) (11), a network of 53 investigators in 43 academic medical centers in 16 countries. The current study involved 31 centers in 10 countries. Data were collected per protocol at enrollment and annually, submitted

to the coordinating center in Halifax, Nova Scotia, Canada and entered into an Access database. Appropriate procedures ensured data quality, management and security. The Nova Scotia Health Authority central zone Research Ethics Board, Halifax, and each of the participating centers' institutional research ethics review boards approved the study.

Patients: Patients fulfilled the ACR classification criteria for SLE (4) which served as the date of diagnosis, and provided written informed consent. Enrollment was permitted up to 15 months following the diagnosis. Demographic variables, education and medication history were collected. Lupus-related variables included the SLE Disease Activity Index 2000 (SLEDAI-2K) (12) and SLICC/ACR damage index (SDI) (13). Laboratory testing required to determine SLEDAI-2K and SDI scores was done at each center.

Neuropsychiatric (NP) events: An enrollment window extended from 6 months prior to the diagnosis of SLE up to the actual enrollment date. NP events were characterized within this window using the ACR case definitions for 19 NP syndromes (14). The clinical diagnosis was supported by investigations, if warranted, as per the guidelines. Patients were reviewed annually with a 6-month window around the assessment date. New NP events and the status of previous NP events since the last study visit were determined at each assessment.

The ACR case definition for psychosis (14) is: (i) delusions or hallucinations without insight; (ii) causing clinical distress or impairment in social, occupational or other relevant areas of functioning; (iii) disturbance should not occur exclusively during delirium; (iv) not better accounted for by another mental disorder. Recurring episodes of psychosis and other NP events within the enrollment window or within a follow-up assessment period were recorded once for that period of observation. The date of the first episode was taken as the onset of the event. Once a NP event had resolved, a subsequent event of the same type was recorded as a new event.

Attribution of NP events: As with other publications on the SLICC NPSLE inception cohort, similar decision rules were used to determine the attribution of NP events (15, 16). Factors considered included: (i) temporal onset of NP event(s) in relation to the diagnosis of SLE; (ii) concurrent non-SLE factor(s), such as potential causes (“exclusions”) or contributing factors (“associations”) for each NP syndrome in the glossary for the ACR case definitions of NP events (14). For psychosis the pre-specified potential alternative causes (“exclusions”) were (a) primary psychotic disorder unrelated to SLE (e.g. schizophrenia); (b) substance or drug induced psychotic disorder; (c) psychologically mediated reaction to SLE (brief reactive psychosis with major stressor), and the pre-specified potential contributing factors (“associations”) were (a) marked psychosocial stress and (b) corticosteroids; (iii) finally “common” NP events in normal population controls as described by Ainiala et al (17) were identified and included isolated headaches, anxiety, mild depression (mood disorders failing to meet criteria for “major depressive-like episodes”), mild cognitive impairment (deficits in less than 3 of the 8 specified cognitive domains) and polyneuropathy without electrophysiological confirmation. Using these three factors,

two attribution decision rules of different stringency (models A and B) were used (15, 16).

Attribution model A (most stringent): NP events which had their onset within the enrollment window and had no “exclusions” or “associations” and were not one of the NP events identified by Ainiola (17) were attributed to SLE.

Attribution model B (least stringent): NP events which had their onset within 10 years of the diagnosis of SLE and were still present within the enrollment window and had no “exclusions” and were not one of the NP events identified by Ainiola (17) were attributed to SLE.

By definition, all NP events attributed to SLE using model A were similarly attributed using model B. Events which did not fulfill these criteria were classified as non-SLE NP events.

Outcome of Psychosis: For every NP event, a physician generated 7-point Likert scale was completed at each follow-up assessment until resolution of the event or patient demise (1=patient demise, 2=much worse, 3=worse, 4=no change, 5=improved, 6=much improved, 7=resolved) (18). A patient generated SF-36 questionnaire was also completed at each assessment and provided subscale, mental (MCS) and physical (PCS) component summary scores (18, 19), that were unavailable to physicians at their assessments.

Autoantibodies: Plasma lupus anticoagulant (LAC), serum IgG anti-cardiolipin, anti- β_2 glycoprotein-I, anti-ribosomal P (anti-P) and anti-NR2 glutamate receptor antibodies were measured at the Oklahoma Medical Research Foundation, USA as described (20-23).

Statistical analysis: Since there were only 15 patients with psychosis attributed to SLE by model A, we used attribution model B and Cox regression to analyze time to first SLE psychosis. This included onset of NP events prior to SLE diagnosis in order to capture all NP events potentially related to the risk of psychosis. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Covariates examined included sex, race/ethnicity, SLICC sites, post-secondary education, number of ACR criteria at enrollment (excluding neurologic disorder), SDI (without NP variables), other concurrent NP events and, as continuous variables, age at SLE diagnosis, disease duration (in years) and SLEDAI-2K (without NP variables). Binary variables indicating autoantibodies present at baseline and follow-up assessments were defined when available. Time-varying variables, other than those related to autoantibodies, were updated at each assessment. When examining the time-varying version of the autoantibody variables, autoantibody data in the period before enrolment were imputed by their values at enrollment, while autoantibody data at follow-up assessments were imputed by the 'last observation carried forward' method. Kaplan-Meier estimates of the survivor function for the time until resolution of psychosis were calculated. For analyses of longitudinal SF-36 subscale and summary scores, linear regression with GEE estimation allowed for correlation of observations within patients and adjustment variables include time/visit, sex, age at SLE diagnosis, race/ethnicity/location, education, SLEDAI-2K and SDI scores

(without NP variables), corticosteroids, antimalarials and immunosuppressant use since last assessment.

Results

Patients: 1,826 patients were recruited between October 1999 and December 2011, from centers in the United States [n=539 (29.5%)], Europe [n=477 (26.1%)], Canada [n=418 (22.9%)], Mexico [n=223 (12.2%)] and Asia [n=169 (9.3%)] (Table 1). The number of patient assessments varied from 1 to 19 with a mean follow-up of 7.4±4.5 years and final assessment follow-up was in March 2017.

Neuropsychiatric (NP) manifestations: NP events (≥ 1) occurred in 951/1,826 (52.1%) patients and 488/1826 (26.7%) had ≥ 2 events over the study period. There were 1902 unique NP events, encompassing all 19 NP syndromes in the ACR case definitions (14). The proportion of NP events attributed to SLE varied from 17.8% (attribution model A) to 31.1% (attribution model B) and occurred in 13.3% (model A) to 21.1% (model B) of patients. Of the 1902 unique NP events, 1742 (91.6%) involved the central nervous system and 160 (8.4%) the peripheral nervous system (14). The classification of events into diffuse and focal was 1471 (77.3%) and 431 (22.7%) respectively (16).

Psychosis: Among 28/1,826 (1.53%) patients with psychosis, 26/28 (93%) had a single psychotic event, while one patient each had 2 and 3 discrete events. The majority of patients had psychosis attributed to SLE [15/28 (54%) using attribution model A and 25/28 (89%) using model B]. Patients with lupus psychosis (model B)

were located in centers from Europe (9 patients), Canada (6 patients), USA (5 patients), Mexico (4 patients) and Asia (1 patient). There was no significant association between location and risk of SLE psychosis ($p=0.53$ in Cox regression) taking the number of patients and the duration of follow-up at each site into account. The majority of patients with lupus psychosis [20/25 (80%)] had their first episode either in the year prior to or within 3 years following the diagnosis of SLE (Figure 1). There were 31 psychotic events of which 16/31 (52%) and 28/31 (90%) were attributed to SLE using attribution model A and B respectively. The earliest psychotic episode occurred 2 months prior to the diagnosis of SLE.

Clinical and laboratory associations with lupus psychosis: Using Cox regression we looked for associations with the risk of the first episode of psychosis attributed to SLE using attribution model B. Univariate analysis revealed a positive association [HR (95%CI)] between male sex [2.58 (1.04,6.41)], younger age at diagnosis (per 10 years, 1.36, (1.0,1.88)], African ancestry [4.80 (1.86,12.40)], in particular for patients outside the United States [5.53 (1.86,16.42)], concurrent other central [3.86 (1.27,11.70)] or diffuse [6.36 (2.12,19.12)] NP events (mood disorder, acute confusional state) attributed to SLE, and presence of anti-ribosomal P antibodies at the enrollment visit into the cohort [3.31 (1.19,9.21)] and over time [3.13 (1.15,8.56)].

Important variables identified in univariate analyses were included in multivariate analyses, excluding antibody variables due to reduced sample size consequent to missing data (Table 2). The significant positive associations [HR (95%CI)] with lupus

psychosis were similar, namely prior SLE NP events [3.59, (1.16,11.14), male sex [3.0, (1.20,7.50)], younger age at SLE diagnosis [per 10 years, 1.45, (1.01,2.07)] and African ancestry [4.59 (1.79,11.76)]. Further, after adjusting for the demographic predictors in Table 2 (sex, age at SLE diagnosis and race/ethnicity), anti-ribosomal P antibodies at enrolment [2.29 (0.81,6.46), $p=0.11$] and over time [2.17 (0.79,5.97), $p=0.13$] were no longer significantly associated with the risk of lupus psychosis

Treatment of SLE psychosis: The treatment of individual patients was at the discretion of their attending rheumatologist and was predicated on the overall needs of the patient and not only the psychotic event. The following therapies were used during the time of the first psychotic events: corticosteroids 23/28 (82.1%) with a mean (SD) dose of prednisone of 21.9 (14.9) mg/day, immunosuppressants (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil) 17/28 (60.7%), biologics 1/28 (3.6%), antipsychotic drugs 19/28 (67.9%), antidepressants 11/28 (39.3%), either/both antipsychotic drugs and antidepressants 22/28 (78.6%). In 13/28 (46.4%) events corticosteroids had been started prior to the onset of psychosis with a mean (SD) dose of 20.3 (13.6).

Clinical outcome and health related quality of life (HRQoL) in patients with lupus psychosis: A summary of physician assessments of outcome of lupus psychosis is illustrated in Figure 2. Over 80% of the psychotic events had resolved by the second annual assessment following onset of the event (Figure 2a). Likewise, the maximum and minimum Likert scores over the duration of follow-up illustrates

that the majority of psychotic events either improved or resolved over the period of observation (Figure 2b).

The mean (SD) SF-36 PCS and MCS scores are shown in Figure 3a for the following four patient groups. Group 1 ($n=29$): visits in patients with onset of lupus psychosis since last assessment or with an ongoing psychotic event; Group 2 ($n=3379$): visits in patients with onset of other NP events since last assessment or ongoing other NP event(s), including non-SLE psychosis; Group 3 ($n=2180$): visits in patients with no NP events since last assessment and no ongoing NP event(s) but with a history of previous NP event(s); Group 4 ($n=5893$): visits in patients who never had NP event(s). The lowest summary scores were in groups 1 and 2 (global $p < 0.001$ in the multivariate analyses) and the negative impact on HRQoL affected all 8 subscales of the SF-36 as show in the accompanying spidergram (Figure 3b).

To determine if there was a persistent change in HRQoL following physician determined resolution of lupus psychosis, patient generated SF-36 scores were compared in the following two groups. Psychosis group ($n=29$): visits in patients with onset of lupus psychosis since last assessment up to its resolution. Resolved group ($n=112$): visits in patients with resolution of lupus psychosis up to their last follow-up or recurrence of psychosis. If the psychotic event had both onset and resolution in the same interval prior to assessment, SF-36 scores at that assessment were included only in the psychosis group. As illustrated in Figure 4a, there was substantial improvement in both MCS scores (mean difference: 7.01) and PCS scores (mean difference: 4.34) and in all subscales of the SF-36 (Figure 4b) concurrent with resolution of lupus psychosis

Discussion

In a large, international, inception cohort study of SLE patients we have prospectively documented the frequency, associations and outcomes of psychotic events over a mean follow-up of 7.4 years. Our findings confirm and expand upon the results of previous cross-sectional and historical studies of psychosis in SLE (6-8, 24, 25). The majority of psychotic events were directly attributed to SLE, had a predilection to occur early in the course of the disease and were more frequent in male patients. Psychosis was also more frequent in those patients of African ancestry as is also the case for non-SLE patients with the same race/ethnicity (26). The outcome of lupus psychosis, as determined by both physicians and patients, was positive and emphasizes the importance of diagnosing and treating this rare manifestation of NPSLE.

Studies of NPSLE conducted prior to the introduction in 1999 of the ACR case definitions for NPSLE did not have a uniform definition for psychosis. Using the ACR case definition, the frequency of psychosis has been reported to vary between 0% and 17.1% (6, 17, 27-30) and in our study it was 1.53% (28/1826). Using a well-defined process for determining attribution, we confirmed that the majority of psychotic events were due to SLE. In keeping with other NPSLE events and with other severe SLE manifestations such as nephritis (31), there was a predilection for psychosis to occur early in the disease course, usually within the first 3 years following the diagnosis of SLE. Univariate analysis identified significant associations between lupus psychosis and anti-ribosomal P antibodies, although following adjustment for demographic variables, the 95% CIs around HRs were wide and included the null value, precluding a definitive conclusion regarding association of

this autoantibody with psychosis. This is consistent with an earlier report on NP events in the SLICC inception cohort (32).

The potential role of corticosteroids must also be considered. In the current study, exposure to corticosteroids prior to lupus psychosis occurred in less than half of the initial events. As per the ACR case definition for psychosis (14), the concurrent use of corticosteroids at the onset of psychosis was identified as an “association” rather than a firm “exclusion”, indicating uncertainty about the role of corticosteroids in individual cases and to allow flexibility for determining attribution. Although NP symptoms have been reported with all types and doses of corticosteroids (33), including psychosis following intra-articular steroid injections (34, 35), in general the dose of corticosteroids is the most important risk factor. In the Boston Collaborative Drug Surveillance Program, the frequency of psychiatric symptoms of any type was 18.6% in patients receiving >80 mg/day of prednisone, 4.6% in patients receiving 41-80 mg/day and 1.3% in those receiving <40 mg/day. In the current study, exposure to corticosteroids prior to lupus psychosis was in the lowest of these dose ranges.

Although the somatic toxicities of corticosteroids are well described, the literature on NP effects is considerably less. Their reported frequency varies widely from 2% to 60% (36-38) and symptoms include affective, behavioural and cognitive manifestations (33). Moreover, the term “steroid psychosis” has been used to capture a heterogeneous group of NP effects, is not supported by validated diagnostic criteria and previous reports have included many patients who were not psychotic. The ACR case definition for psychosis (14), used in the current study, is based upon the Diagnostic and Statistical Manual of Mental Disorders, Fourth

Edition (DSM-IV) (39). In a previous study of 2,069 patients who received corticosteroids only 3 (0.14%) developed psychosis using DSM-IV criteria (40).

One of the major advantages of our prospective study was the ability to document the short-term impact and long-term outcome of lupus psychosis from the perspective of both the physician and patient. In keeping with previous studies (6, 7) the physician assessments indicated resolution in the majority of cases with very few recurrences. Using a previously validated approach to measure the clinical outcome of NP events in SLE (18) we used summary and subscale scores of the SF-36 to assess the patient perspective. This is important because physician and patient assessment of outcome for other manifestations of SLE (41) and some NP events (42) may be discrepant. Although the greatest impact was on MCS scores it was apparent that all subscales of the SF-36 were negatively impacted in patients with lupus psychosis. However, following treatment and in keeping with physician assessment of outcome, the patient generated SF-36 scores showed a remarkable reversal when averaged over time.

There are some limitations to the current study. First, the small number of patients with lupus psychosis limited our ability to precisely estimate potential associations with clinical or laboratory variables of interest. However, most of the previous studies have had an even smaller sample size and the SLICC cohort is the largest inception cohort of SLE patients. Second, specialized investigations such as advanced neuroimaging or cytokine profiling of CSF were not routinely performed but left to the discretion of individual investigators which reflects what is done in clinical practice, a

key component of our overall SLICC protocol. Third, the observational cohort study design precludes determination of optimal therapeutic regimes for lupus psychosis but rather reflects current standard of care. Despite these limitations, the study provides encouraging data on the outcome of this rare but potentially devastating manifestation of NPSLE.

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Legends for Figures

Figure 1: The relationship between the time of onset of lupus psychosis and diagnosis of SLE.

Figure 2: Physician determined outcome of lupus psychosis. A: Survival curves for resolution. B: The highest and lowest Likert scale scores over the duration of follow-up are shifted to the right indicating improvement.

Figure 3: Association of SF-36 summary and subscale scores with lupus psychosis.

A: mean (SD) physical component summary (PCS) and mental component summary (MCS) scores in 4 patient groups. Group 1 ($n=29$): visits in patients with onset of

lupus psychosis since last assessment or with an ongoing psychotic event; Group 2 ($n=3379$): visits in patients with onset of other NP events since last assessment or ongoing other NP event(s), including non-SLE psychosis; Group 3 ($n=2180$): visits in patients with no NP events since last assessment and no ongoing NP event(s) but with a history of previous NP event(s); Group 4 ($n=5893$): visits in patients who never had NP event(s). The number of assessments contributing to each bar are aggregated for patients over time.

B: comparison of individual subscale scores in the same 4 patient groups. The SF-36 subscales are VT = Vitality, SF = Social function, RE = Role emotion, MH = Mental health, PF = Physical function, RP = Role physical, BP = Bodily pain, GH= General health.

Figure 4: The long term change in SF-36 summary and subscale scores following resolution of lupus psychosis.

A: mean (SD) physical component summary (PCS) and mental component summary (MCS) scores in 2 patient groups. Psychosis group ($n=29$): visits in patients with onset of lupus psychosis since last assessment up to its resolution. Resolved group ($n=112$): visits in patients with resolution of lupus psychosis up to their last follow-up or recurrence of psychosis. If the psychotic event had both onset and resolution in the same interval prior to assessment, SF-36 scores at that assessment were included only in the psychosis group. The number of assessments contributing to each bar are aggregated for patients over time.

B: comparison of individual subscale scores in the same 2 patient groups. The SF-36 subscales are VT = Vitality, SF = Social function, RE = Role emotion, MH = Mental health, PF = Physical function, RP = Role physical, BP = Bodily pain, GH= General health.

Table 1: Demographics, clinical features, medications, autoantibodies at enrolment.

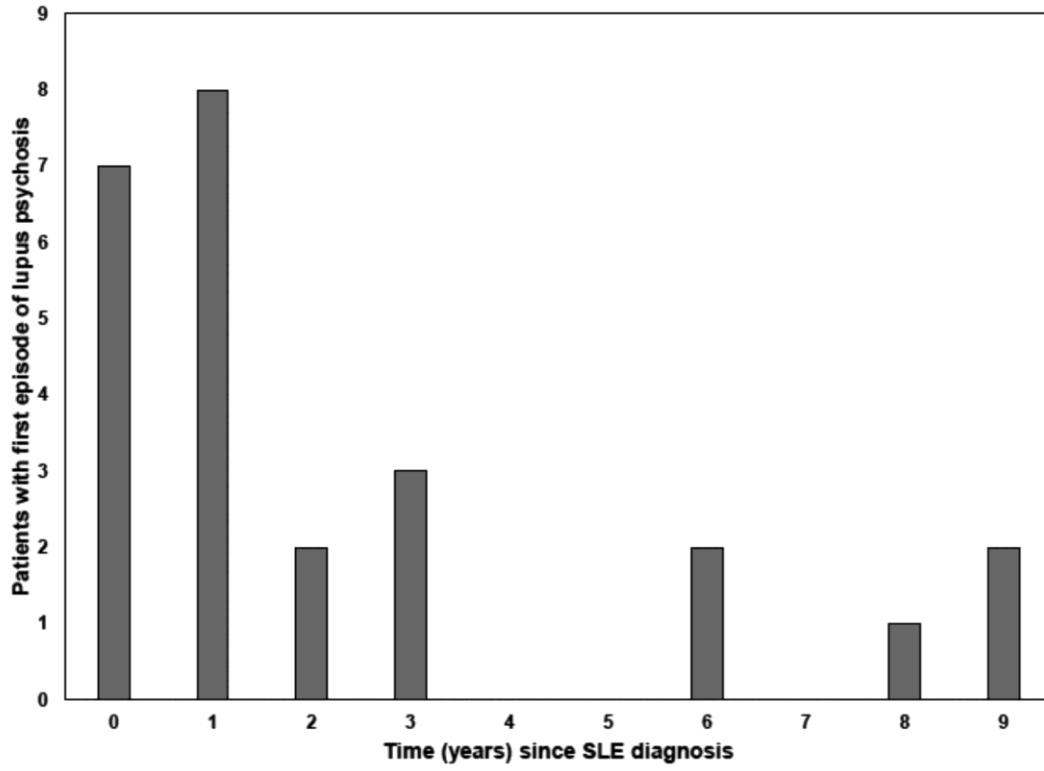
Number of Patients		1826
Sex (%)	Female	1622 (88.8)
	Male	204 (11.2)
Age (years) (mean \pm SD)		35.1 \pm 13.3
Race/Ethnicity (%)	Caucasian	891 (48.8)
	African	306 (16.8)
	Hispanic	282 (15.4)
	Asian	275 (15.1)
	Other	72 (3.9)
Single/Married/Other (%)		818 (44.9)/766 (42.0)/238 (13.1)
Post-secondary education (%)		1064 (61.9)
Disease duration (months) (mean \pm SD)		5.6 \pm 4.2
Number of ACR criteria (mean \pm SD)		4.9 \pm 1.1
ACR manifestations (%)	Malar rash	660 (36.1)
	Discoid rash	227 (12.4)
	Photosensitivity	652 (35.7)
	Oral/nasal ulcers	677 (37.1)
	Serositis	502 (27.5)
	Arthritis	1368 (74.9)
	Renal disorder	510 (27.9)
	Neurological disorder	88 (4.8)
	Hematologic disorder	1129 (61.8)
	Immunologic disorder	1392 (76.2)
	Antinuclear antibody	1731 (94.8)
	SLEDAI-2K score (mean \pm SD)	
*SLICC/ACR damage index score (mean \pm SD)		0.32 \pm 0.74
Medications (%)	Corticosteroids	1284 (70.3)
	Antimalarials	1231 (67.4)

	Immunosuppressants	732 (40.1)
	ASA	261 (14.3)
	Antidepressants	183 (10.0)
	Warfarin	99 (5.4)
	Anticonvulsants	80 (4.4)
	Antipsychotics	12 (0.7)
Autoantibody positivity N (%)	Lupus anticoagulant	241/1174 (20.5)
	Anti-cardiolipin	138/1142 (12.1)
	Anti-Beta2 glycoprotein-I	163/1142 (14.3)
	Anti-ribosomal P	112/1136 (9.9)
	Anti-NR2	130/1064 (12.2)

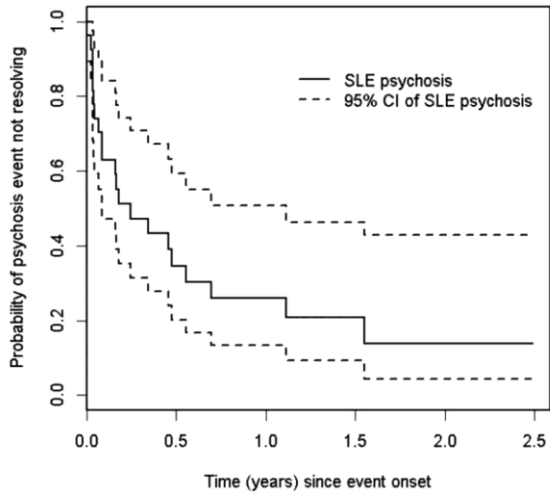
*SLICC/ACR damage index not available in 1057 patients at enrollment visit when disease duration < 6 months

Table 2: Predictors of lupus psychosis by multivariate analysis.

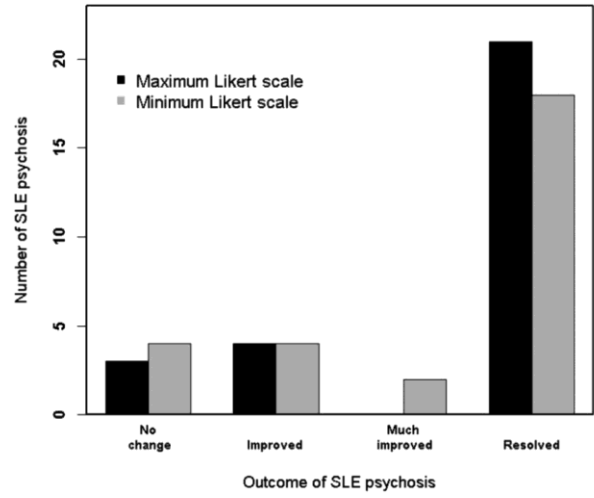
Predictor	Factor level	Hazard Ratio	95% HR	95% HR	p (Wald)
Other Concurrent NP events	No concurrent NP events	1			
	Any unresolved NP events attributed to SLE	3.59	1.16	11.14	0.027
	Any unresolved NP events not attributed to SLE but no events attributable to SLE	0.89	0.21	3.82	0.087
	Global (Wald) test				0.082
Sex	Female	1			
	Male	3.0	1.20	7.50	0.019
Age at SLE diagnosis/10		0.69	0.48	0.99	0.044
RACE	Caucasian	1			
	African	4.59	1.79	11.76	0.002
	Asian and Other	0.93	0.24	3.64	0.913
	Hispanic	1.37	0.39	4.85	0.622
	Global (Wald) test				0.005



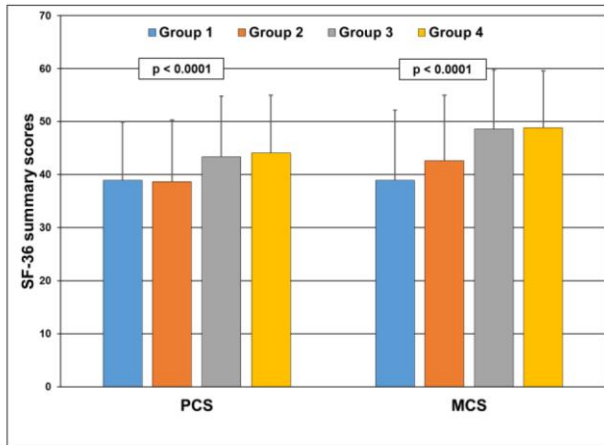
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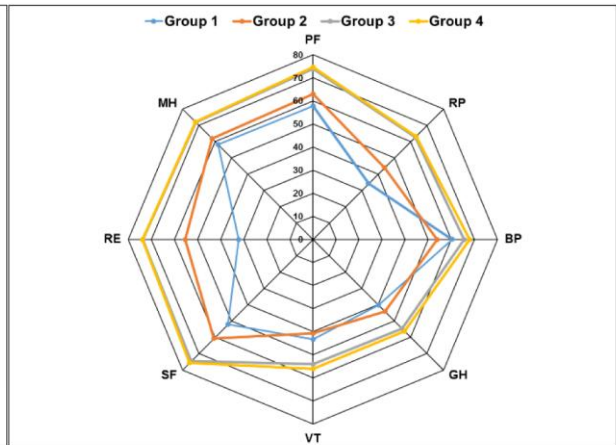
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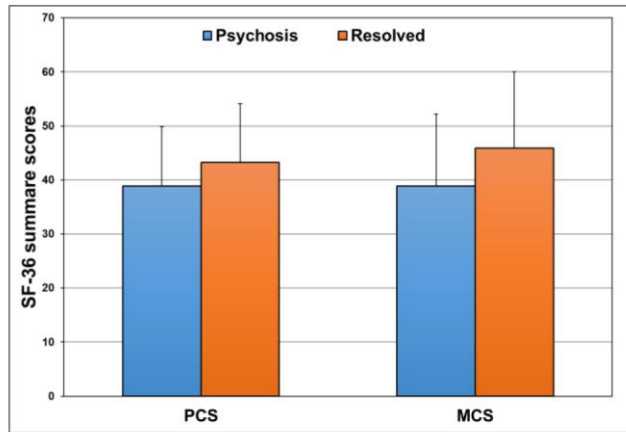
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B

