# Exploring the risk factors and prognosis of transverse myelitis in systemic lupus erythematosus

**Minhui Wang, Ziqian Wang, Li Zhang, Jiuliang Zhao, Di Wu, Jing Li, Qian Wang, Jinmei Su, Dong Xu, Shangzhu Zhang, Mengtao Li** (ID) **and Xiaofeng Zeng**

## Abstract

**Purpose:** We aimed to describe the clinical characteristics and outcomes of patients with transverse myelitis (TM) as a rare manifestation in systemic lupus erythematosus (SLE) and explore the risk factors and prognosis of SLE-related TM (SLE-TM).

**Methods:** We conducted a retrospective case–control and cohort analysis. All patients with SLE-TM (58 patients) and 232 with SLE without TM, as a control group, were admitted to Peking Union Medical College Hospital between January 1993 and May 2021. Factors associated with the presence of SLE-TM and its prognosis were assessed using logistic regression and Cox proportional hazard models.

**Results:** Multivariate analysis revealed that positive anti-Ro/Sjogren's syndrome A (anti-Ro/ SSA) ($<$0.01) and increased erythrocyte sedimentation rate (ESR) ($p < 0.01$) were associated with SLE-TM. Regarding prognosis, methylprednisolone (MP) pulse therapy within 2 weeks of onset (adjusted hazard ratio (AHR), 2.12; 95% confidence interval (CI), 1.06–4.23; $p = 0.03$) was associated with short-term neurological improvement. An American Spinal Injury Association Impairment Scale (AIS) grades of A, B, or C at onset (AHR, 0.12; 95% CI 0.05–0.28; $p < 0.001$) and hypoglycorrhachia (AHR, 0.29; 95% CI, 0.13–0.65; $p < 0.01$) were associated with a short-term non-improved outcome.

**Conclusions:** The positive anti-Ro/SSA antibodies and increased ESR may be associated with the presence of SLE-TM. An initial presentation with severe myelitis and hypoglycorrhachia appear to be predictors of a poor neurological outcome. Early steroid pulse therapy may improve the prognosis.

*Keywords:* systemic lupus erythematosus, transverse myelitis, risk factors, prognosis

## Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can affect multiple organs and systems. Transverse myelitis (TM), a rare but serious SLE manifestation, is characterized by an acutely progressive course of paralysis, sensory deficit, and sphincter dysfunction. The estimated incidence rate of TM is 1–2% in patients with SLE,[1–3] although the reported rate varies widely between studies.

As the overall incidence rate of TM is low, the risk factors for this SLE manifestation remain unknown. The SLE-related TM (SLE-TM) prognosis also requires further elucidation since current prognostic evidence comes from case series and a few retrospective cohort studies.[4–7] Understanding the risk and prognostic factors of TM may increase recognition of this low-incidence disease and facilitate early diagnosis, allowing administration of timely aggressive treatment, which may reduce disability in patients with SLE-TM.[1,6]

Therefore, this study aimed to investigate the risk factors and prognosis for SLE-TM in a large

Correspondence to:
**Shangzhu Zhang**
Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology

State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH)

Key Laboratory of Rheumatology, and Clinical Immunology, Ministry of Education, Beijing, 100730, China.
**irenezhangpumch@163.com**

**Mengtao Li**
Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science & Technology

State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital (PUMCH)

Key Laboratory of Rheumatology, and Clinical Immunology, Ministry of Education, Beijing, 100730, China.
**mengtao.li@cstar.org.cn**

**Minhui Wang**
**Ziqian Wang**
**Li Zhang**
**Jiuliang Zhao**
**Di Wu**
**Jing Li**
**Qian Wang**
**Jinmei Su**
**Dong Xu**
**Xiaofeng Zeng**
Department of
Rheumatology and Clinical
Immunology, Peking Union
Medical College Hospital,
Chinese Academy of
Medical Sciences & Peking
Union Medical College

National Clinical Research
Center for Dermatologic
and Immunologic Diseases
(NCRC-DID), Ministry of
Science & Technology

State Key Laboratory of
Complex Severe and Rare
Diseases, Peking Union
Medical College Hospital
(PUMCH)

Key Laboratory of
Rheumatology, and
Clinical Immunology,
Ministry of Education,
Beijing, China

clinical population to inform risk factor modification, prognostication, and treatment strategies.

## Methods

### Research design

To study the risk factors of SLE-TM, we used a case–control analysis. In addition, we chose a retrospective cohort study design to explore the prognostic factors and relapse rates of SLE-TM. The study followed guidance from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[8] The Research Ethics Committee of the Peking Union Medical College Hospital approved this study on September 1, 2021 (approval no. S-F1745).

### Study participants

Patients with SLE-TM were identified from the Peking Union Medical College Hospital between January 1993 and May 2021. All patients with SLE-TM met the Transverse Myelitis Consortium Working Group[9] definition of myelitis. Those with TM related to central nervous system infections, multiple sclerosis, and structural lesions, including tumor metastasis, herniated disk, or vertebral fracture, were excluded. Furthermore, all patients fulfilled the 1997 American College of Rheumatology (ACR) revised criteria[10] or the ACR/Systemic International Collaborating Clinics (SLICC) 2012 criteria.[11] The patients in the control group were extracted by random sampling technique from the SLE patients without TM, which was confirmed by a follow-up period starting at the first admission in our hospital and ending at the date of the latest medical record. Sample size was calculated considering that the sample size should be >10–20 times the number of independent variables to be added into the model[12] in the SLE-TM and control groups, as well as considering $\alpha = 0.5$ and power = 80%. Finally, data from 58 patients with SLE-TM and 232 controls (1:4) were analyzed. Our study de-identified all patients' details, and we obtained patients informed written consent in the choice of treatments, such as glucocorticoids pulse therapy or immunosuppressants.

### Definitions

At the time of admission and follow-up visits, neurological deficits were assessed by a neurologist and a rheumatologist using the American Spinal Injury Association Impairment Scale (AIS), which is stratified from A (no sensory or motor function below the level of spinal injury) to E (normal sensory and motor function).[13] The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was adopted to evaluate SLE disease activity at the time of TM diagnosis.[14] The SLICC/ACR Damage Index (SDI), which includes 12 organ systems, was used to evaluate organ damage of SLE patients.[15] Longitudinal extensive TM (LETM) was defined as a spinal cord lesion extending over ≥3 vertebral segments.[16] Patients were considered to have neuromyelitis optica spectrum disorder (NMOSD) simultaneously with SLE-TM when the 2015 international consensus diagnostic criteria for NMOSD were fulfilled.[17] Definition of high-risk anti-phospholipid (aPL) antibodies' profiles was that the presence (in two or more occasions at least 12 weeks apart) of lupus anticoagulant (LA), or of double (any combination of LA, anticardiolipin (aCL) antibodies or anti-β2-glycoprotein I (anti-β2GPI) antibodies) or of triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titers. Low-risk aPL profile included isolated aCL or anti-β2GPI antibodies at low–medium titers, particularly if transiently positive.[18] Hyperproteinorachia was defined as a protein level >0.45 g/L in the cerebrospinal fluid (CSF). Hypoglycorrhachia was defined as a glucose level <2.8 mmol/L or <50% of the blood glucose level in the CSF. AIS classifications of A, B, or C at initial presentation were classified as severe myelitis.[6] The occurrence of relapse of myelitis during the follow-up period, defined as TM-compatible neurological symptoms confirmed by magnetic resonance imaging (MRI) after a period of neurological improvement, was also evaluated. The follow-up period was defined as the time from first onset of myelitis to the last follow-up or relapse. All patients were closely followed up during the first 3 months. The main endpoint was neurological impairment (AIS grade) during the first 3 months. An unfavorable neurological outcome was defined as an AIS grades A, B, or C at follow-up. In addition, patients with at least one-grade improvement in AIS after treatment were classified as improved outcomes, while the non-improved outcome included patients with permanent neurological impairment.

### Data for analysis

Data were extracted from the medical records for analysis. Clinical data for SLE-TM patients and

non-SLE-TM patients were retrospectively collected at the time of admission, including demographic data (sex, age at enrollment, SLE duration, and TM duration), systemic manifestations, physical signs (including neurological signs), and laboratory examinations that included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement, and self-antibodies status. CSF was collected, and biochemical analyses and MRI were performed. Information concerning treatment and prognosis was also compiled. Anti-nuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) were tested by indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA). Anti-Ro/Sjogren's syndrome A (Anti-R0/SSA), anti-La/Sjogren's syndrome B (anti-La/SSB), anti-Smith (anti-Sm), anti-ribosomal P protein (anti-rRNP), and anti-U1 ribonucleoprotein (anti-RNP) antibodies were tested by dot blotting. Serum titers of aPL, including aCL and anti-β2GPI antibodies were measured using standardized commercial ELISA kits. LA activity was tested by the integrated activated partial thromboplastin time test.

### Statistical analysis

The characteristics of patients with SLE-TM and those with SLE without TM (controls) are summarized as mean (*SD*), median (first and third quartiles), or number (percentage). Given the retrospective collection of data and the observational nature of the study, some data were incomplete. Missing data were not imputed. The control population was selected randomly, reducing the risk of selection bias. We used nonparametric analysis because the continuous variables were not normally distributed. Associations between categorical or continuous variables and TM were examined using the chi-square and Mann–Whitney *U* tests. We used multivariable logistic regression models to calculate the odds ratios (OR) and 95% confidence intervals (CIs) and assess the association between specific factors and SLE-TM. A logistic regression model was used with all the potential factors to ascertain the factors for the risk of SLE-TM. We explored factors associated with short-term (3-month) prognosis of SLE-TM using a logistic regression model and Cox proportional hazard regression to calculate the OR and hazard ratio (HR). Regarding short-term neurological improvement, we used Cox proportional hazard regression to estimate HR adjusted for the underlying confounding variables. The

Kaplan–Meier method was used to draw the remission curve and calculate the cumulative remission rate. A *p* value $< 0.05$ was set for statistical significance.

All statistical analyses were performed using the 19th version of SPSS software (IBM Inc.) and STATA 15 (Stata Corporation, College Station, TX, USA).

## Results

### Demographic and clinical characteristics

Fifty-eight patients with SLE-TM were included in the study group. The median age at TM onset was 34.5 years (interquartile range (IQR), 25.75–45.25 years). TM presented as one of the initial manifestations of SLE in 8/58 (13.8%) cases. The most common neurological presentation of TM was symmetrical flaccid paraparesis (39.7%), with anesthesia or hypoesthesia (31.0%), and sphincter dysfunction (70.7%). SLE-TM patients with an initial TM presentation were classified according to their neurological deficits, by AIS grade: grade A, 10/58 (17.2%) patients; grade B, 8/58 (13.8%); grade C, 5/58 (8.6%); and grade D, 35/58 (60.3%). Concomitant NMOSD was present in 25/49 (51.0%) cases. The clinical characteristics, treatment regimens, and outcomes of these patients are described in Tables 1 and 2.

### Laboratory and imaging results

Laboratory test results, including CSF results, and imaging findings are presented in Tables 2 and 3. A positive aCL screen occurred in 11/56 (19.6%) patients, anti-β2GPI in 9/51 (17.6%), and LA antibodies were present in 15/54 (27.8%). The most frequent positive antibody at the time of TM diagnosis was anti-Ro/SSA, identified in 37/58 (63.8%) patients, followed by anti-dsDNA in 36/58 (62.1%) patients. Spinal cord MRI was performed in 56/58 patients at baseline. LETM was observed in 40/56 (71.4%) of the patients, with the thoracic spine being the most common site of involvement (18/56), followed by the cervical spine (15/56).

### Treatments and outcomes

Intravenous methylprednisolone (MP) pulse therapy was administered to 53/58 (91.4%) patients, 500–1,000 mg for 3–5 days. This

**Table 1.** Demographic and clinical features of SLE-TM.

|  | *N* = 58 (%) |
|---|---|
| Features of SLE |  |
| Female | 56 (96.6) |
| Age at myelitis onset (years) | 34.50 (25.75–45.25) |
| SLE duration (years) | 2.00 (0.00–7.25) |
| TM after SLE diagnosis | 50 (86.2) |
| Cutaneous involvement | 8/55 (14.5) |
| Musculoskeletal involvement | 10/55 (18.2) |
| Pleuritis | 9/55 (16.4) |
| Pericarditis | 8/55 (14.5) |
| Renal involvement | 24 (41.4) |
| Hematological involvement | 25 (43.1) |
| SLEDAI-2K | 9.50 (4.00–16.00) |
| SDI | 1.00 (1.00–1.00) |
| Features of TM |  |
| TM as the first symptom | 8 (13.8) |
| Paraparesis | 23 (39.7) |
| Sensory deficit | 18 (31.0) |
| Sphincter dysfunction | 41 (70.7) |
| Severe myelitis at onset | 23 (39.7) |
| Concomitant NMOSD | 25/49 (51.0) |

SLE, systemic lupus erythematosus; TM, transverse myelitis; NMOSD, neuromyelitis optica spectrum disorder; SDI, Systemic International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, the Systemic Lupus Erythematosus Disease Activity Index 2000.

treatment was provided within 2 weeks of TM onset in 36/58 (62.1%) patients, within 4 weeks of TM onset in 43/58 (74.1%), and after >4 weeks of TM onset in 15/58 (25.9%). Cyclophosphamide (CTX) was administered to 42/58 (72.4%) patients. Other treatments provided included immunoglobulin therapy in 27/58 (46.6%) patients and rituximab in 12/52 (23.1%). All 58 patients had a recorded AIS grade at the 3-month follow-up, with neuropsychiatric functional improvement attained in 45/58 (77.6%) patients and non-improvement in 13/58 (22.4%). In addition, an unfavorable outcome (AIS grades A, B, or C) was observed in 18/58 (31.0%) patients and a favorable outcome in 40/58 (69.0%).

### Risk factors associated with SLE-TM

We constructed an analysis of 58 SLE-TM cases and 232 controls. Compared with the controls, SLE-TM patients had a higher prevalence of increased ESR, SDI and positive anti-Ro/SSA, anti-La/SSB, and anti-RNP antibodies ($p < 0.05$) (Table 3). The multivariate analysis (Table 4) revealed that anti-Ro/SSA positive (OR, 2.68; 95% CI, 1.35–5.31; $p < 0.01$) and increased ESR (OR, 3.73; 95% CI, 1.71–8.17; $p < 0.01$) were

**Table 2.** Laboratory, imaging, and treatment features of SLE-TM.

| | *N* = 58 (%) |
|---|---|
| Laboratory results | |
| Hyperproteinorachia | 40 (69.0) |
| Hypoglycorrhachia | 16 (27.6) |
| Imaging results | |
| LETM | 40/56 (71.4) |
| Affected segments | |
| Thoracic | 18/56 (32.1) |
| Cervical | 15/56 (26.8) |
| Treatment | |
| MP pulse | 53 (91.4) |
| MP pulse within 2 weeks | 36 (62.1) |
| MP pulse within 4 weeks | 43 (74.1) |
| CTX | 42 (72.4) |
| RTX | 12/52 (23.1) |
| Follow-up time (years) | 2.00 (0.25–5.00) |

CTX, cyclophosphamide; LETM, longitudinal extensive transverse myelitis; MP, methylprednisolone; RTX, rituximab. Hyperproteinorachia refers to a protein level < 0.15 g/L in the cerebrospinal fluid. Hypoglycorrhachia was defined as a glucose level <2.8 mmol/L or <50% of the blood glucose level in the cerebrospinal fluid.

considered as risk factors for the presence of SLE-TM.

*Prognostic factors for SLE-TM patients*
The analysis of prognostic factors included all 58 patients with SLE-TM whose neurological outcome (AIS grade) had been assessed at 3 months (Table 5). An AIS grades of A, B, or C at onset ($p < 0.001$) and hypoglycorrhachia ($p < 0.001$) were associated with an unfavorable prognosis. MP pulse therapy within 2 weeks of onset ($p < 0.01$) was considered a protective factor for neurological outcomes. In the multivariate logistic regression analysis, no obvious factors were associated with an unfavorable neurological outcome of SLE-TM.

When considering neurological improvement at 3 months (Table 6), age at TM diagnosis ($p = 0.02$), an initial presentation with severe myelitis ($p < 0.001$) (Figure 1), hypoglycorrhachia ($p = 0.001$), and MP pulse within 2 weeks ($p < 0.01$) (Figure 2) were significantly associated with neurological improvement. Finally, the analysis where we adjusted for age at myelitis showed that MP pulse therapy within 2 weeks of onset (adjusted hazard ratio (AHR), 2.12; 95% CI, 1.06–4.23; $p = 0.03$) was associated with short-term neurological improvement. An American Spinal Injury AIS grades of A, B, or C at onset (AHR, 0.12; 95% CI 0.05–0.28; $p < 0.001$) and hypoglycorrhachia (AHR, 0.29; 95% CI, 0.13–0.65; $p < 0.01$) were associated with a short-term non-improved outcome.

*Relapse rates of SLE-TM patients*
The median follow-up time of all the patients is 2.00 years (IQR, 0.25–5.00 years). The 1-, 3- and 5-year relapse rates were 18.42% (7/38) (95% CI, 0.08–0.34), 37.04% (10/27) (95% CI, 0.19–0.58) and 56.25% (9/16) (95% CI, 0.30–0.80), respectively.

**Table 3.** Characteristics between the SLE cases with transverse myelitis and controls.

| | TM patients (*N* = 58) (%) | Controls (*N* = 232) (%) | *p* value |
|---|---|---|---|
| Age at SLE onset (years) | 29.00 (21.50–41.50) | 27.12 (21.51–35.88) | 0.41 |
| Female | 56 (96.6) | 213 (91.8) | 0.34 |
| Elevated ESR | 49 (84.5) | 136 (58.6) | **<0.001** |
| Elevated CRP | 19 (32.8) | 59/175 (33.7) | 0.89 |
| Hypocomplementemia | 34 (58.6) | 138 (59.5) | 0.91 |
| Autoantibody profiles | | | |
|   Anti-dsDNA | 36 (62.1) | 118 (50.9) | 0.13 |
|   Anti-Sm | 8 (13.8) | 59 (25.4) | 0.06 |
|   Anti-Ro/SSA | 37 (63.8) | 78 (33.6) | **<0.001** |
|   Anti-La/SSB | 15 (25.9) | 23 (9.9) | **0.001** |
|   Anti-RNP | 20 (34.5) | 45 (19.4) | **0.014** |
|   Anti-rRNP | 11 (19.0) | 48 (20.7) | 0.77 |
|   aPL and different aPL profiles | | | |
|     aCL | 11/56 (19.6) | 35 (15.1) | 0.40 |
|     Anti-β2GP1 | 9/51 (17.6) | 50 (21.6) | 0.53 |
|     LA | 15/54 (27.8) | 35 (19.3) | 0.18 |
| SLEDAI-2K | 9.50 (4.00–16.00) | 8.00 (3.00–13.00) | 0.14 |
| SDI | 1.00 (1.00–1.00) | 0.00 (0.00–0.00) | **<0.001** |

SLE, systemic lupus erythematosus; TM, transverse myelitis; aPL, anti-phospholipid antibodies; aCL, anti-cardiolipin antibodies; anti-β2GP1, anti-beta 2 glycoprotein 1 antibodies; LA, lupus anticoagulation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SDI, Systemic International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, the Systemic Lupus Erythematosus Disease Activity Index 2000.

## Discussion

As SLE-TM is rare, our current understanding of the underlying prognostic factors of TM is based on small sample-sized studies, and to the best of our knowledge, we are the first to explore the factors for SLE-TM risk. This study is the largest to date to have evaluated underlying factors for risk and prognosis of SLE-TM. Anti-Ro/SSA positivity and increased ESR may be associated with the presence of SLE-TM. Moreover, an initial presentation with severe myelitis (AIS grades A, B, or C at onset), hypoglycorrhachia, and delayed steroid pulse treatment appear to predict a worse neurological prognosis.

Previous studies revealed that most of the patients developed TM after the diagnosis of SLE,[1,4,19–21] which is easy to identify the cause. Nevertheless, in our studies, TM was the initial complaint in 8/58 (13.8%) patients. In these cases, it would be essential to diagnose the underlying SLE for prompt and adequate treatment. Hence, immunological screening for SLE, including ANA, anti-dsDNA, anti-Sm, and aPL antibodies screening, should be considered for patients presenting with TM.

The current understanding of the pathogenic mechanism of SLE-TM is limited to injuries

**Table 4.** Factors associated with the risk of SLE-TM.

| | Univariate logistic regression | | Multivariate logistic regression | |
|---|---|---|---|---|
| | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| Characteristics | | | | |
|   Age at SLE onset (years) | 1.01 (0.99–1.04) | 0.39 | | |
|   Elevated ESR | 3.84 (1.80–8.20) | **<0.001** | 3.73 (1.71–8.17) | **<0.01** |
|   Elevated CRP | 0.96 (0.51–1.80) | 0.89 | | |
|   Hypocomplementemia | 0.97 (0.54–1.73) | 0.91 | | |
| Autoantibody profiles | | | | |
|   Anti-dsDNA | 1.58 (0.88–2.85) | 0.13 | | |
|   Anti-Sm | 0.47 (0.21–1.05) | 0.07 | | |
| Anti-Ro/SSA | 3.48 (1.91–6.34) | **<0.001** | 2.68 (1.35–5.31) | **<0.01** |
| Anti-La/SSB | 3.17 (1.53–6.57) | **<0.01** | 1.99 (0.85–4.62) | 0.11 |
| Anti-RNP | 2.19 (1.16–4.11) | **0.02** | 1.98 (0.99–3.84) | 0.06 |
|   Anti-rRNP | 0.90 (0.43–1.86) | 0.77 | | |
|   aPL and different aPL profiles | | | | |
|     aCL | 1.38 (0.65–2.92) | 0.41 | | |
|     Anti-β2GP1 | 0.78 (0.36–1.71) | 0.54 | | |
|     LA | 1.60 (0.80–3.23) | 0.19 | | |
| SLEDAI-2K | 1.02 (0.98–1.06) | 0.27 | | |

SLE, systemic lupus erythematosus; TM, transverse myelitis; aPL, anti-phospholipid antibodies; aCL, anti-cardiolipin antibodies; anti-β2GP1, anti-beta 2 glycoprotein 1 antibodies; LA, lupus anticoagulation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SDI, Systemic International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, the Systemic Lupus Erythematosus Disease Activity Index 2000.

resulting from vascular pathologies, including inflammatory or embolic/thrombotic/ischemic conditions. Some researchers believe that an autoimmunologic process is dominant, while others have postulated on the presence of thrombosis, fibrinoid arteries, perivasculitis, spinal cord softening, and peripheral white-matter degeneration at multiple spinal cord levels as causes of SLE-TM.[22,23] The presence of aPL antibodies always were considered as a possible etiology of SLE-TM through their thromboembolic effects on the microcirculation of the spine.[24] However, the clinical value of aPL in SLE-TM remains controversial.[5,7,25] In our review of the literature, although the presence or absence of aPL was examined in the development of SLE-TM, the individual profiles of aPL (LA, aCL, and anti-β2GPI) have not been considered. Nevertheless, we found that aPL and different aPL profiles results were not predictive of the presence of the TM and short-term TM prognosis. Therefore, the role of aPL and different aPL profiles as risk and prognostic factors for SLE-TM is not yet clear and needs to be further investigated.

Anti-Ro/SSA positivity may be potential risk factors for the presence of SLE-TM in our study. Precious study showed that the target protein of anti-Ro/SSA antibodies also played an important role in the regulation of inflammation in lupus.[26]

**Table 5.** Prognostic factors for unfavorable neurological outcome[a] of transverse myelitis.

| | Univariate logistic regression | |
| --- | --- | --- |
| | OR (95% CI) | *p* value |
| Characteristics | | |
| Age at myelitis onset | 0.95 (0.90–1.00) | 0.05 |
| SLEDAI-2K | 1.02 (0/94–1.1) | 0.67 |
| SDI | 0.28 (0.03–2.44) | **0.25** |
| Neurological impairment | | |
| AIS A/B/C at onset | 152.00 (19.67–1175.01) | <**0.001** |
| Laboratory findings | | |
| Hyperproteinorachia | 3.00 (0.74–12.11) | 0.12 |
| Hypoglycorrhachia | 18.00 (4.33–74.76) | <**0.001** |
| Hypocomplementemia | 1.64 (0.51–5.23) | 0.83 |
| Increased CRP | 2.11 (0.66–6.73) | 0.21 |
| Increased ESR | 4.25 (0.49–36.87) | 0.19 |
| Autoantibody profiles | | |
| Anti-dsDNA positive | 0.67 (0.22–2.10) | 0.49 |
| Anti-Sm | 0,71 (0.13–3.91) | 0.69 |
| Anti-Ro/SSA | 0.60 (0.19–1.88) | 0.38 |
| Anti-La/SSB | 0.75 (0.20–2.80) | 0.67 |
| Anti-RNP | 1.32 (0.42–4.20) | 0.64 |
| Anti-rRNP | 1.35 (0.34–5.35) | 0.67 |
| aPL and different aPL profiles | | |
| aCL | 0.44 (0.09–2.32) | 0.34 |
| Anti-β2GP1 | 0.25 (0.03–2.20) | 0.21 |
| LA | 0.93 (0.24–3.54) | 0.91 |
| Low-risk aPL profile | 2.38 (0.31–18.36) | 0.41 |
| High-risk aPL profile | 0.53 (0.15–1.92) | 0.34 |
| Spinal cord MRI | | |
| LETM | 2.60 (0.64–10.64) | 0.18 |
| Affected segments | | |
| Thoracic | 0.80 (0.28–2.26) | 0.67 |
| Treatment | | |
| MP pulse within 2 weeks | 0.17 (0.05–0.56) | <**0.01** |
| CTX | 1.50 (0.41–5.51) | 0.54 |

AIS, American Spinal Injury Association Scale; CRP, C-reactive protein; CTX, cyclophosphamide; ESR, erythrocyte sedimentation rate; LETM, longitudinal extensive transverse myelitis; MP, methylprednisolone; SDI, Systemic International Collaborating Clinics/ American College of Rheumatology Damage Index; SLEDAI-2K, the Systemic Lupus Erythematosus Disease Activity Index 2000; TM, transverse myelitis.
[a]An unfavorable neurological outcome was defined as an AIS grade A, B, or C at follow-up.

**Table 6.** Prognostic factors for improvement outcome[a] of myelitis within 3 months of follow-up.

| | HR (95% CI) | | Adjusted[b] | p value |
|---|---|---|---|---|
| | **Unadjusted** | **p value** | | |
| Characteristics | | | | |
|    Age at myelitis onset | 1.03 (1.00–1.06) | **0.02** | 1 (reference) | 1 (reference) |
|    SLEDAI-2K | 0.99 (0.95–1.03) | 0.57 | | |
|    SDI | 1.41 (0.65–3.04) | 0.38 | 1.07 (0.48–2.40) | 0.86 |
| Neurological impairment | | | | |
|    AIS A/B/C at onset | 0.11 (0.05–0.26) | **<0.001** | 0.12 (0.05–0.28) | **<0.001** |
| Laboratory findings | | | | |
|    Hyperproteinorachia | 0.60 (0.32–1.12) | 0.11 | | |
|    Hypoglycorrhachia | 0.26 (0.12–0.59) | **0.001** | 0.29 (0.13–0.65) | **<0.01** |
|    Hypocomplementemia | 0.733 (0.40–1.33) | 0.31 | | |
|    Increased CRP | 0.84 (0.43–1.60) | 0.59 | | |
|    Increased ESR | 0.56 (0.26–1.22) | 0.14 | | |
|    Anti-dsDNA positive | 0.87 (0.48–1.57) | 0.64 | | |
|    Anti-Sm positive | 0.81 (0.36–1.81) | 0.60 | | |
| Anti-Ro/SSA positive | 1.22 (0.65–2.30) | 0.54 | | |
| Anti-La/SSB positive | 1.10 (0.57–2.13) | 0.78 | | |
| Anti-RNP positive | 0.61 (0.33–1.14) | 0.12 | | |
|    Anti-rRNP positive | 0.88 (0.41–1.89) | 0.74 | | |
| aPL and different aPL profiles | | | | |
|    aCL positive | 1.02 (0.49–2.13) | 0.96 | | |
|    Anti-β2GP1 positive | 1.30 (0.60–2.85) | 0.50 | | |
|    LA positive | 0.98 (0.50–1.91) | 0.96 | | |
|    Low-risk aPL profile | 0.42 (0.10–1.75) | 0.23 | | |
|    High-risk aPL profile | 1.12 (0.60–2.09) | 0.73 | | |
| Spinal cord MRI | | | | |
|    LETM | 0.68 (0.36–1.30) | 0.25 | | |
|    Affected segments | | | | |
|       Thoracic | 1.68 (0.90–3.13) | 0.11 | | |
| Treatment | | | | |
|    MP pulse within 2 weeks | 2.44 (1.25–4.76) | **<0.01** | 2.12 (1.06–4.23) | 0.03 |
|    CTX | 0.80 (0.42–1.52) | 0.49 | | |

AIS, American Spinal Injury Association Scale; CRP, C-reactive protein; CTX, cyclophosphamide; ESR, erythrocyte sedimentation rate; LETM, longitudinal extensive transverse myelitis; MP, methylprednisolone; SDI, Systemic International Collaborating Clinics/ American College of Rheumatology Damage Index; SLEDAI-2K, the Systemic Lupus Erythematosus Disease Activity Index 2000; TM, transverse myelitis.
[a]An improved neurological outcome was defined as at least one-grade improvement in AIS after treatment.
[b]Adjusted HR indicates hazard ratio adjusted for age at myelitis.
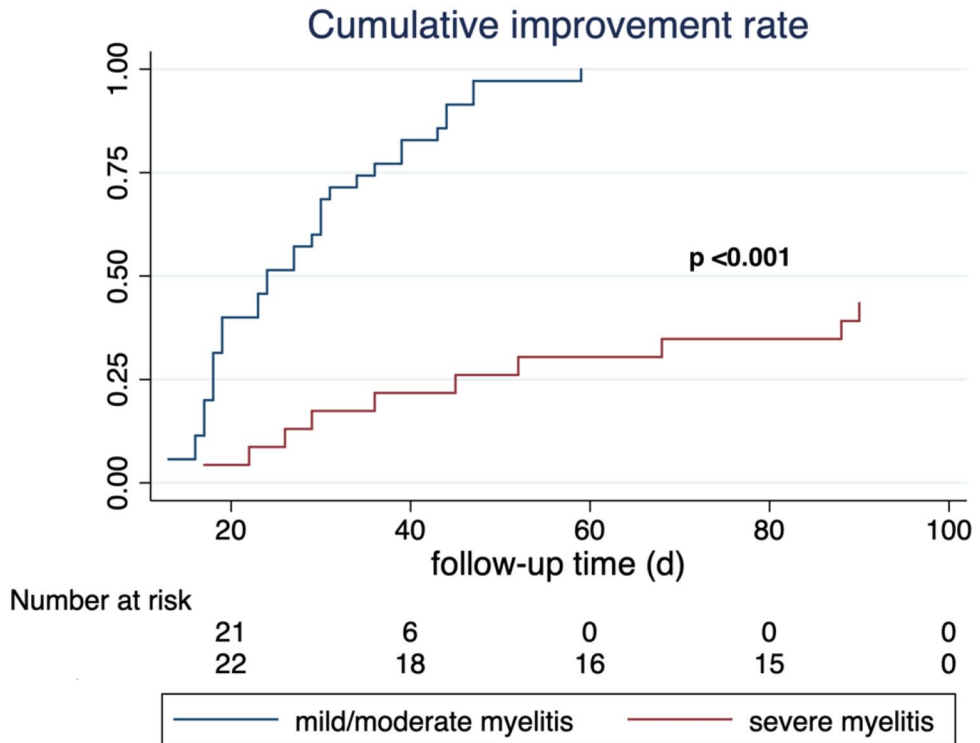
**Figure 1.** Kaplan–Meier survival curves of systemic lupus erythematosus patients with transverse myelitis for severe myelitis-cause cumulative improvement rate.
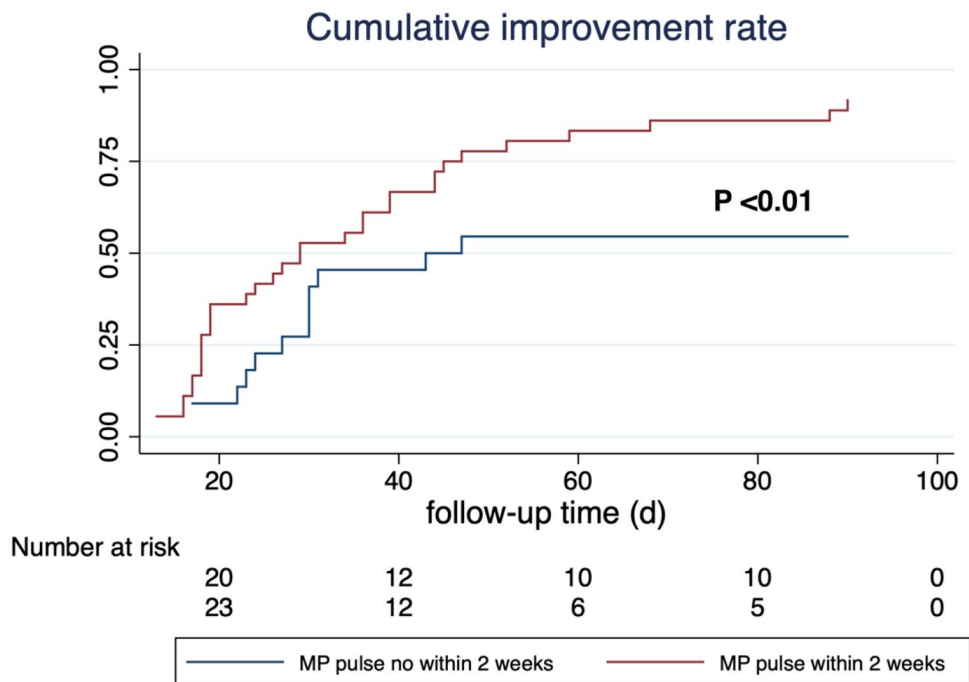


**Figure 2.** Kaplan–Meier survival curves of systemic lupus erythematosus patients with transverse myelitis for methylprednisolone pulse within 2-week-cause cumulative improvement rate.

Similarly, the presence of anti-Ro/SSA antibodies in SLE-TM has been shown to predict a relapse in the disease course.[23] Some studies have associated the presence of anti-Ro/SSA antibodies with the development of neuropsychiatric lupus erythematosus (NPSLE).[27] The value of anti-Ro/SSA positivity in the pathogenesis of SLE-TM remains unclear and anti-Ro/SSA antibodies requires further study.

Hypoglycorrhachia appears to be associated with an unfavorable neurological prognosis in this study. Undoubtedly, glucose metabolism is of great importance in central nervous function. Studies have found focal infiltration of the spinal cord by monocytes and CD4+ and CD8 + T lymphocytes, accompanied by activation of astrocytes and microglia in TM patients.[28] CD4+ T-cells and proinflammatory microglia exert biological function by glycolysis, which relies on high levels of glucose uptake.[29–32] Thus, hypoglycorrhachia is considered to be a hallmark of inflammatory activity. It may give an indication of the underlying mechanisms of TM-related nerve injury in SLE. High-quality evidence is limited, and the exact pathogenesis awaits further exploration in future studies.

The initial severity of myelitis may be a strong predictive factor of SLE-TM prognosis. Most recovery occurs within the first 3 months from symptom onset, but improvement could continue for ⩾1 year. Our study could therefore provide risk stratification for TM management for those patients with severe myelitis and/or in the presence of hypoglycorrhachia who are at high risk of poor prognosis[4,5] may need to be treated more aggressively in the early stage. Notably, we did not identify a strong correlation between anti-dsDNA, hypocomplementemia, or SLEDAI scores and TM prognosis, which were reported in previous studies.[4,6,25] Differences in the sample populations across studies may have contributed to the noted contradiction.

MRI of the spine is very helpful as a diagnostic method to confirm SLE-TM.[33,34] In our study, the most commonly affected region was the thoracic spine.[19,35] We noticed that abnormality on the MRI was not always consistent with clinical manifestations. In our analysis, LETM was not found to be associated with a worse prognosis. However, the exact value of MRI findings, currently, in patients with SLE-TM is inconsistent, with heterogeneous findings having been reported, including 'normal' MRIs in patients with severe SLE-TM.[21,36,37]

Glucocorticoids combined with immunosuppressants provide a basis to treat the inflammatory manifestations of SLE. However, there is no strong evidence for the optimal treatment because most are derived from case studies or extrapolation from trials involving TM patients with other etiologies. Nevertheless, we still propose that early aggressive treatment may be crucial for a favorable response.[38,39] The possible window period for the likelihood of a better outcome of SLE-TM was within 2 weeks of the onset of TM symptoms, using glucocorticoids pulse therapy. Early induction therapy, using high doses of glucocorticoids combined with CTX, has been used as the standard first-line treatment for SLE-TM.[40] Saison *et al.*[6] reported that non-use of CTX was associated with unfavorable neurological outcomes in SLE-TM. However, we did not identify a specific effect of CTX on the prognosis of neurological outcomes in our study. Apart from the differences in sample populations, the time window from the onset of TM to the initiation of treatment, as well as appropriate administration of CTX at an adequate dose at TM onset may be an explanatory factor. Concerning anticoagulation therapy, a previous study did not show a positive effect on neurological outcomes of SLE-TM, even among aPL-positive patients. Furthermore, since the characteristics of TM (ischemic or vasculitic) are not easy to define, the effects of anti-aggregation or anticoagulation treatment would be a worthwhile subject for further study more carefully before drawing any solid conclusion.

Approximately, half of the SLE-TM patients have a combination of NMOSD in our cohort. However, the exact relationship between SLE-TM and NMOSD remains controversial. An international expert panel concluded that SLE in NMOSD is a coexistence rather than a complication.[17] This conclusion was mainly based on the fact that in patients with NMOSD and SLE, the central nervous system lesions are secondary to an astrocytopathy from AQP4-IgG, rather than the vasculitis found in SLE. Nevertheless, this hypothesis is inconsistent because NMOSD could occur in the context of established SLE,[41] which is also demonstrated in our study. Therefore, the relationship between NMOSD and SLE warrants further study before definite conclusions are reached.

TM is typically monophasic but relapsing TM within several months of the first event in 21–55% of patients.[42] Our studies have revealed that the 1-, 3- and 5-year relapse rates were 18.42% (95% CI, 0.08–0.34), 37.04% (95% CI, 0.19–0.58), and 56.25% (95% CI, 0.30–0.80), respectively. It can be seen clearly that the recurrence rate is relatively high in lupus myelitis, worth prompt treatment and monitoring the conditions closely.

### Strengths

Our study has several strengths. First, it is the largest SLE-TM cohort to have been evaluated to date. Second, this is the first study to explore the risk factors for lupus-related myelitis. Finally, our findings may yield hypotheses on the risk and prognosis of SLE-TM, contributing to evidence on the prediction of risk and prognosis of SLE-TM to inform future research and clinical practice.

### Limitations

First, this was an observational retrospective study in nature. Second, this was a relatively small sample size. Hence, the statistical power could have been weakened, especially in prognostic analysis. Third, both the case and the control groups included inpatients. Therefore, the potential selection bias was inevitable. In addition, the lack of widespread use of scales, such as AIS, especially by non-neurologists, would lead to the absence of long-term neurological prognosis assessment.

### Conclusion

The positive anti-Ro/SSA antibodies and increased ESR may be risk factors for the presence of SLE-TM. An initial presentation with severe myelitis and hypoglycorrhachia might be predictors of a poor neurological outcome. Early aggressive treatment with MP pulse may improve the prognosis.

### Acknowledgements

The authors thank the Department of Rheumatology at the Peking Union Medical College Hospital for providing the database.

### Availability of data and materials

All authors and all reviewer had availability of these data and materials.

### Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital. All patients from our center provided written informed consent in accordance with the Declaration of Helsinki.

### Consent for publication

Authors consent for publication.

### Author contributions

### Funding

## Conflict of interest statement

## ORCID iD

Mengtao Li ⓘD https://orcid.org/0000-0003-4252-2889

## Supplemental material

Supplemental material for this article is available online.

## References

1. Kovacs B, Lafferty TL, Brent LH, *et al.* Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. *Ann Rheum Dis* 2000; 59: 120–124.

2. West SG. Neuropsychiatric lupus. *Rheum Dis Clin North Am* 1994; 20: 129–158.

3. Bhat A, Naguwa S, Cheema G, *et al.* The epidemiology of transverse myelitis. *Autoimmun Rev* 2010; 9: A395–A399.

4. Chiganer EH, Lessa CF, Di Pace JL, *et al.* Transverse myelitis in systemic lupus erythematosus: clinical features and prognostic factors in a large cohort of Latin American patients. *J Clin Rheumatol* 2021; 27: S204–S211.

5. Ahn SM, Hong S, Lim DH, *et al.* Clinical features and prognoses of acute transverse myelitis in patients with systemic lupus erythematosus. *Korean J Intern Med* 2019; 34: 442–451.

6. Saison J, Costedoat-Chalumeau N, Maucort-Boulch D, *et al.* Systemic lupus erythematosus-associated acute transverse myelitis: manifestations, treatments, outcomes, and prognostic factors in 20 patients. *Lupus* 2015; 24: 74–81.

7. Lu X, Gu Y, Wang Y, *et al.* Prognostic factors of lupus myelopathy. *Lupus* 2008; 17: 323–328.

8. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; 12: 1495–1499.

9. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology* 2002; 59: 499–505.

10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.

11. Petri M, Orbai AM, Alarcón GS, *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64: 2677–2686.

12. Norman G, Monteiro S and Salama S. Sample size calculations: should the emperor's clothes be off the peg or made to measure? *BMJ* 2012; 345: e5278.

13. Kirshblum SC, Waring W, Biering-Sorensen F, *et al.* Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. *J Spinal Cord Med* 2011; 34: 547–554.

14. Gladman DD, Ibañez D and Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29: 288–291.

15. Gladman DD, Urowitz MB, Goldsmith CH, *et al.* The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 809–813.

16. Bertsias GK, Ioannidis JP, Aringer M, *et al.* EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis* 2010; 69: 2074–2082.

17. Wingerchuk DM, Banwell B, Bennett JL, *et al.* International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; 85: 177–189.

18. Tektonidou MG, Andreoli L, Limper M, *et al.* EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 2019; 78: 1296–1304.

19. Quintanilla-González L, Atisha-Fregoso Y, Llorente L, *et al.* Myelitis in systemic lupus erythematosus: clinical characteristics and effect in accrual damage. A single-center experience. *Lupus* 2017; 26: 248–254.

20. Costallat BL, Ferreira DM, Costallat LT, *et al.* Myelopathy in systemic lupus erythematosus: clinical, laboratory, radiological and progression findings in a cohort of 1,193 patients. *Rev Bras Reumatol Engl Ed* 2016; 56: 240–251.

21. Espinosa G, Mendizábal A, Mínguez S, *et al.* Transverse myelitis affecting more than 4 spinal segments associated with systemic lupus erythematosus: clinical, immunological, and radiological characteristics of 22 patients. *Semin Arthritis Rheum* 2010; 39: 246–256.

22. Provenzale J and Bouldin TW. Lupus-related myelopathy: report of three cases and review of the literature. *J Neurol Neurosurg Psychiatry* 1992; 55: 830–835.

23. Li XY, Xiao HB and Pai P. Myelitis in systemic lupus erythematosus. *J Clin Neurosci* 2017; 44: 18–22.

24. Birnbaum J, Petri M, Thompson R, *et al.* Distinct subtypes of myelitis in systemic lupus erythematosus. *Arthritis Rheum* 2009; 60: 3378–3387.

25. Oiwa H, Kuriyama A, Matsubara T, *et al.* Clinical value of autoantibodies for lupus myelitis and its subtypes: a systematic review. *Semin Arthritis Rheum* 2018; 48: 214–220.

26. Boccitto M and Wolin SL. Ro60 and Y RNAs: structure, functions, and roles in autoimmunity. *Crit Rev Biochem Mol Biol* 2019; 54: 133–152.

27. Borowoy AM, Pope JE, Silverman E, *et al.* Neuropsychiatric lupus: the prevalence and autoantibody associations depend on the definition: results from the 1000 faces of lupus cohort. *Semin Arthritis Rheum* 2012; 42: 179–185.

28. Krishnan C, Kaplin AI, Deshpande DM, *et al.* Transverse myelitis: pathogenesis, diagnosis and treatment. *Front Biosci* 2004; 9: 1483–1499.

29. Frauwirth KA, Riley JL, Harris MH, *et al.* The CD28 signaling pathway regulates glucose metabolism. *Immunity* 2002; 16: 769–777.

30. Wang R, Dillon CP, Shi LZ, *et al.* The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity* 2011; 35: 871–882.

31. Jacobs SR, Herman CE, Maciver NJ, *et al.* Glucose uptake is limiting in T cell activation and requires CD28-mediated Akt-dependent and independent pathways. *J Immunol* 2008; 180: 4476–4486.

32. Wang L, Pavlou S, Du X, *et al.* Glucose transporter 1 critically controls microglial activation through facilitating glycolysis. *Mol Neurodegener* 2019; 14: 2.

33. Kenik JG, Krohn K, Kelly RB, *et al.* Transverse myelitis and optic neuritis in systemic lupus erythematosus: a case report with magnetic resonance imaging findings. *Arthritis Rheum* 1987; 30: 947–950.

34. Tartaglino LM, Croul SE, Flanders AE, *et al.* Idiopathic acute transverse myelitis: MR imaging findings. *Radiology* 1996; 201: 661–669.

35. D'Cruz DP, Mellor-Pita S, Joven B, *et al.* Transverse myelitis as the first manifestation of systemic lupus erythematosus or lupus-like disease: good functional outcome and relevance of antiphospholipid antibodies. *J Rheumatol* 2004; 31: 280–285.

36. Boumpas DT, Patronas NJ, Dalakas MC, *et al.* Acute transverse myelitis in systemic lupus erythematosus: magnetic resonance imaging and review of the literature. *J Rheumatol* 1990; 17: 89–92.

37. Monahan RC, Beaart HJL, Fronczek R, *et al.* Suspected transverse myelitis with normal MRI and CSF findings in a patient with lupus: what to do? A case series and systematic review. *Neuropsychiatr Dis Treat* 2020; 16: 3173–3186.

38. Sherer Y, Hassin S, Shoenfeld Y, *et al.* Transverse myelitis in patients with antiphospholipid antibodies – the importance of early diagnosis and treatment. *Clin Rheumatol* 2002; 21: 207–210.

39. Harisdangkul V, Doorenbos D and Subramony SH. Lupus transverse myelopathy: better outcome with early recognition and aggressive high-dose intravenous corticosteroid pulse treatment. *J Neurol* 1995; 242: 326–331.

40. Fanouriakis A, Kostopoulou M, Alunno A, *et al.* 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78: 736–745.

41. Martín-Nares E, Hernandez-Molina G and Fragoso-Loyo H. Aquaporin-4-IgG positive neuromyelitis optica spectrum disorder and systemic autoimmune diseases overlap syndrome: a single-center experience. *Lupus* 2019; 28: 1302–1311.

42. Schulz SW, Shenin M, Mehta A, *et al.* Initial presentation of acute transverse myelitis in systemic lupus erythematosus: demographics, diagnosis, management and comparison to idiopathic cases. *Rheumatol Int* 2012; 32: 2623–2627.