



The role of anti-ribosomal P autoantibodies in the prediction of neuropsychiatric damage in systemic lupus erythematosus based on CSTAR cohort (XIV)

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Abstract

Objectives To identify the predictive value of anti-ribosomal P protein (anti-RibP) antibodies on the accrual of neuropsychiatric damage in systemic lupus erythematosus (SLE) patients in a large cohort in the Chinese SLE Treatment and Research group (CSTAR) database.

Methods This single-center prospective study was conducted based on data from the CSTAR registry. At baseline, we collected demographic characteristics, autoantibody profiles, clinical manifestations, disease activity status, and organ damage. Follow-up data were collected by reviewing clinical records and telephone interviews. Anti-RibP antibodies were identified by immunoblot containing all three native RibP (P0, P1, P2) antigenic proteins.

Results Of 2395 SLE patients with complete follow-up data, 659 (27.5%) were anti-RibP antibody positive. At baseline, positive anti-RibP antibodies were associated with a higher proportion of neurological involvement ($P < 0.05$). During follow-up, patients with positive anti-RibP antibodies were more likely to accumulate neuropsychiatric damage (adjusted HR = 3.8, 95% CI 2.7–57), $p < 0.001$). What is more, the cumulative probability of new-onset neurological involvement increased gradually in anti-RibP antibody-positive patients.

Conclusion Anti-RibP antibodies can provide information about not only organ involvement at baseline, but also neuropsychiatric damage accrual and new-onset neurological involvement during follow-up. We suggested that anti-RibP antibody detection should be done in the newly diagnosed SLE patients to predict organ involvement and even the accumulation of neuropsychiatric damage.

Key Points

- Positive anti-RibP antibodies were associated with baseline neurological involvement.
- Baseline positive anti-RibP antibodies can predict the neuropsychiatric damage accrual and new-onset neurological involvement.

Keywords Autoantibodies · Anti-RibP antibody · Organ damage · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by generation of autoantibodies [1]. Autoantibodies are closely associated with clinical manifestations and disease activity [2]. Among those SLE-related autoantibodies, anti-dsDNA antibody and anti-Sm antibody have been widely used in clinical diagnosis of SLE [3] and their relationship with organ involvement have

been well studied [4]. Besides, other autoantibodies are also important in SLE pathogenesis [5]. Some were regarded as potential biomarkers to predict organ involvement and inform effective treatments [6]. Anti-ribosomal P protein (anti-RibP) antibodies direct to 3 ribosomal phosphoproteins (P0, P1, and P2) and are highly specific for SLE. Multiple studies have demonstrated that anti-RibP antibodies are associated with neuropsychiatric lupus erythematosus (NPSLE) [7], lupus hepatitis [8], and lupus nephritis (LN) [9]. With improvement in SLE survival, prevention of cumulative organ damage became a major goal in SLE management since it affects mortality and quality of life [10, 11]. However, the predictive value of the anti-RibP antibodies on organ damage has not been well studied due to the small case number. Therefore, in this single-center prospective study, we aimed to investigate the predictive value of anti-RibP antibodies on the accumulation of organ damage and probability of new-onset neurological involvement in a large CSTAR-based cohort of Chinese SLE patients.

Methods

Patients and follow-up

Chinese SLE treatment and research (CSTAR) is the first multi-center Chinese SLE cohort composed of 104 rheumatology centers from 30 provinces in China [12]. CSTAR launched in 2009 and has already described the major demographic and clinical manifestations of SLE patients [13]. Based on this prospective cohort, we consecutively collected 2516 patients registered in CSTAR and diagnosed SLE at Peking Union Medical College Hospital (PUMCH, the biggest center of CSTAR) from January 2006 to June 2020. All the patients fulfilled the revised American College of Rheumatology (ACR) classification criteria for SLE (1997) [14] or 2012 classification criteria of the Systemic Lupus International Collaborating Centers (SLICC) group [15]. Patients without autoantibody profile data were excluded (48 patients). After enrollment, all patients were followed up at the clinic. The loss to follow-up was defined as follows: the patient never revisited PUMCH and could not be contacted, or he or she chose to discontinue participation after enrollment. This study was approved by the Institute Review Board of PUMCH (Approval number, S-197).

Data collection and follow-up

The time of recruitment (baseline) was defined as the time of SLE diagnosis. We collected the baseline data through CSTAR online registry, including demography, clinical manifestations, laboratory data, Disease Activity Index 2000 (SLEDAI) [16], and Systemic Lupus International

Collaborating Clinics/American College of Rheumatology damage index (SDI) [17]. Clinical records were reviewed to collect follow-up data, mainly for SDI at the individual organ systems and the occurring time of new organ damage. Telephone interviews were employed to supply additional data for analysis. We defined the end-point as the occurrence of new organ damage or the latest follow-up. Time in the Kaplan-Meier survival analysis for new organ damage in anti-RibP antibody-positive and anti-RibP antibody-negative patients was measured from baseline to end-point.

Measures

The clinical manifestations in our study included malar rash, discoid skin lesions, photosensitivity, arthritis, oral ulcerations, alopecia, serositis, vasculitis, nephropathy, neurological involvement, and hematological involvement. Neurological involvement was defined as seizures, psychosis mononeuritis multiplex, vasculitis myelitis, peripheral or cranial neuropathy, or acute confusional state in the absence of offending drugs or known metabolic derangements [15]. Nephropathy was defined clinically (persistent proteinuria > 0.5 grams per day or cellular casts) [15] or histologically (renal biopsy compatible with LN histopathology classes I, II, III, IV) [18]. Hematologic involvement was defined as hemolytic anemia with reticulocytosis or leukopenia (< 4000/mm³ on ≥ 2 occasions) or lymphopenia (< 1500/mm³ on ≥ 2 occasions) or thrombocytopenia (< 100,000/mm³) in the absence of offending drugs. SLEDAI [16] was used to assess disease activity. SDI, which covers 12 organ systems, was adopted to evaluate organ damage of SLE patients [17]. Neuropsychiatric damage was defined as an increase of at least one point in the neural domain of the SDI damage index, including cognitive impairment or major psychosis, seizures requiring therapy for 6 months, cerebrovascular accident, cranial or peripheral neuropathy (excluding optic), and transverse myelitis. Cognitive impairment included memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, and impaired performance level. Other neuropsychiatric damages were diagnosis through neuroimaging, including brain MRI/MRA (magnetic resonance angiography), and/or electrophysiological studies [19].

The autoantibodies were all measured at the lab of PUMCH with the same assays. Anti-nuclear antibody (ANA) was detected by indirect immunofluorescence (IIF) assay with Hep-2 cell line from Euroimmun AG (Lübeck, Germany). Anti-dsDNA antibody was tested by IIF using flagellate protozoa substrates and enzyme-linked immunosorbent assay (ELISA) using IMTEC ds-DNA Antibodies ELISA KT (Human Worldwide, Wiesbaden, Germany). Anti-extractable nuclear antigen (ENA) antibodies were tested with the immunoblotting assay using the EUROLINE

ENA Profile 9 Ag (Euroimmun) according to the manufacturer’s instructions. Anti-RibP antibodies were identified by immunoblot containing all three native RibP (P0, P1, P2) antigenic proteins. The antiphospholipid (aPL) antibodies, including IgG or IgM anticardiolipin antibodies, anti-β2 glycoprotein I, and lupus anticoagulant, were tested using ELISA (anticardiolipin and anti-β2 glycoprotein I antibody) or dilute Russell viper venom test (lupus anticoagulant).

Statistical analyses

Descriptive statistics are presented as frequency for categorical variables and median ± standard deviations (SD) for continuous variables. Chi-square tests were performed to identify the association between baseline clinical manifestations and anti-RibP antibodies. We adopted univariable and multivariate regression analysis of the cox proportional hazard model to determine the prediction value of anti-RibP antibodies on organ damage accumulation. The Kaplan-Meier method was used for survival analysis, and the log-rank test was adopted to compare the survival rates between the anti-RibP antibody–positive and anti-RibP antibody–negative groups. The results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). All tests of significance were two-sided, and a *P* value of < 0.05 was considered statistically significant. Statistical analysis was performed by using SPSS 24.0 (IBM, Armonk, NY, USA) and R Statistical Software, version 3.6.1. (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline clinical manifestations of SLE patients

In this prospective study, 2516 SLE patients were enrolled. Among them, 121 (4.8%) patients were lost to follow-up after recruitment. Included in further analysis were 2395 patients with complete follow-up data (163 males and 2232 female patients). The presence of anti-RibP antibodies in this study was 27.5% (659/2395) (Table 1). No correlation was found between the reactivity of anti-RibP antibodies and other antibodies (Fig. 1).

The association between anti-RibP antibodies and baseline clinical manifestations

The association analysis revealed that, compared with negative anti-RibP antibodies patients, patients with positive anti-RibP antibodies had a higher rate of neurological involvement (24.6% vs 19.4%, *P* < 0.05), malar rash (45.8%

Table 1 The baseline characteristics, profile of autoantibodies, and profile of clinical manifestations of 2395 SLE patients

	Number (%) or mean ± SD
Female, <i>n</i> (%)	2232 (93.2)
Age at diagnosis (years), mean ± S.D.	33.4±10.9
Disease duration (years), mean ± S.D.	7.8±5.5
SLEDAI, mean ± S.D.	3.3±4.8
Malar rash, <i>n</i> (%)	1053 (44.0)
Discoid lesions, <i>n</i> (%)	276 (11.5)
Arthritis, <i>n</i> (%)	1245 (52.0)
Ulcerations, <i>n</i> (%)	542 (22.6)
Serositis, <i>n</i> (%)	426 (17.8)
Alopecia, <i>n</i> (%)	973 (40.6)
Nephropathy, <i>n</i> (%)	1237 (51.6)
Hematological involvement, <i>n</i> (%)	1417 (59.2)
Neurological involvement, <i>n</i> (%)	499 (20.8)
Anti-nuclear antibody (ANA), <i>n</i> (%)	2395 (100.0)
Anti-double stranded DNA (anti-dsDNA) antibody, <i>n</i> (%)	1609 (67.3)
Anti-Sm antibody, <i>n</i> (%)	767 (32.1)
Anti-RNP antibody, <i>n</i> (%)	1092 (45.7)
Anti-SSA antibody, <i>n</i> (%)	1458 (60.9)
Anti-SSB antibody, <i>n</i> (%)	435 (18.2)
Anti-ribosomal P protein (anti-RibP) antibody, <i>n</i> (%)	659 (27.5)
Anti-nucleosome antibody (ANuA), <i>n</i> (%)	599 (25.0)
Anti-histone antibody (AHA), <i>n</i> (%)	492 (20.5)
Anti-phospholipid (APL) antibodies, <i>n</i> (%)	735 (30.7)

vs 38.7%, *P* < 0.05), photosensitivity (7.1% vs 4.6%, *P* < 0.05), alopecia (45.8% vs 38.7%, *P* < 0.05), and arthritis (55.5% vs 50.5%, *P* < 0.05) at baseline (Table 2).

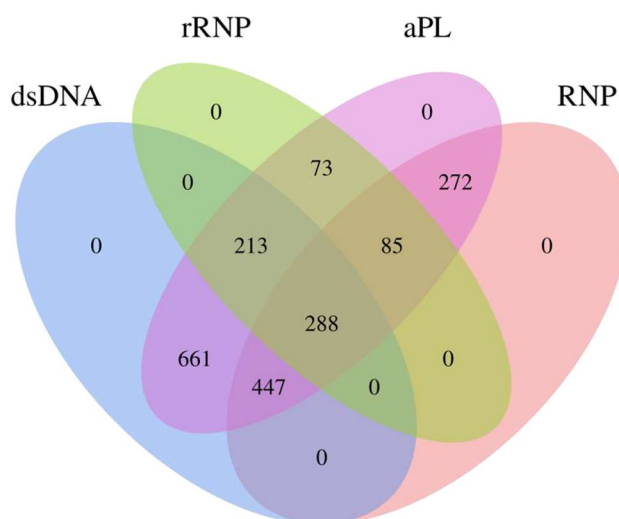


Fig. 1 The association between anti-RibP antibodies and other antibodies

Table 2 Clinical manifestations in patients with or without the presence of anti-RibP antibodies

	+(n = 659)	-(n = 1736)	p
Clinical manifestations, n (%)			
Malar rash	368(55.8)	685(39.5)	<0.001
discoid lesions	77(11.7)	199(12.5)	0.880
photosensitivity	47(7.1)	79(4.6)	0.012
Arthritis	366(55.5)	879(50.5)	0.032
ulcerations	157(23.8)	3852(2.2)	0.390
Serositis	121(18.4)	3051(7.6)	0.651
Alopecia	302(45.8)	675(38.7)	0.001
Nephropathy	338(51.3)	899(51.8)	0.828
Hematological involvement	395(59.9)	1022(58.9)	0.635
Neurological involvement	162(24.6)	337(19.4)	0.005

Survival analysis

The predictive value of anti-RibP antibodies on organ damage accrual

During the follow-up, 279 (11.65%) increases of SDI damage index occurred. The mean (\pm SD) time of follow-up was 4.9 (\pm 4.1) years. To identify the association between anti-RibP antibodies and irreversible organ damage, univariable cox regression analyses were carried out. Only items that included more than 20 patients were compared. As shown in Table 3, patients with positive anti-RibP antibodies were more often develop neuropsychiatric damage (HR = 5.79, 95% CI 4.05–8.27, $P < 0.001$) and avascular necrosis (HR = 2.03, 95% CI 1.05–3.92, $P < 0.001$) during the follow-up period than those with negative one. When the neuropsychiatric damage item was divided into its components, cognitive impairment (HR = 4.59, 95% CI 2.36–8.30, $P < 0.001$) and cerebral vascular (HR = 2.89, 95% CI 1.79–4.66, $P < 0.001$) were more common in anti-RibP antibody-positive patients. Besides neuropsychiatric damage, anti-RibP antibodies were also the risk factor of avascular necrosis (HR = 2.03, CI 1.05–3.92, $P < 0.001$).

As shown in Fig. 2, there were significant differences between the neuropsychiatric damage accumulation of anti-RibP antibody-positive and anti-RibP antibody-negative patients (log-rank test, $p < 0.05$). To further identify the predictive value of anti-RibP antibodies on neuropsychiatric damage accrual, we carried out multivariable cox regression model (Table 3). Potential confounding factors included age at visit (years), sex, aPL antibodies, and baseline organ damage > 0. Besides positive anti-RibP antibodies, patients with younger age (HR = 0.97, 95% CI 0.94–0.99, $p < 0.05$), positive aPL antibodies (HR = 1.8, 95% CI 1.3–2.7, $p < 0.05$), and presence of organ damage at baseline (HR = 1.5, 95% CI 1.3–1.8, $p < 0.001$) were also associated

with neuropsychiatric damage accrual. After accounting for potential confounders, anti-RibP antibodies remained independently associated with increased neuropsychiatric damage accrual (adjusted HR = 3.8, 95% CI 2.7–5.7, $p < 0.001$).

The cumulative probability of new-onset neurological involvement in anti-RibP antibody-positive patients

As shown in Table 2, among the 659 patients with positive anti-RibP antibodies, 162 patients showed neurological involvement at baseline. The other 497 patients without neurological involvement at baseline were included in the sub-group analysis. The follow-up period was 11.5 years, as all the new-onset neurological involvement occurred during this period. The rate of appearance of neurological involvement gradually increased during the follow-up period (Fig. 3). Patients with positive anti-RibP antibodies were more likely to develop neurological involvement than those with negative ones (log-rank test, $p < 0.05$). Before the endpoint, 12.1% (60/497) anti-RibP antibody-positive patients develop neurological symptoms, which was higher than that in anti-RibP antibody-negative patients (1.9%, 26/1389).

Discussion

In this study, we identified the role of anti-RibP antibodies in SLE in a large prospective cohort (2395). We confirmed the associations between anti-RibP antibodies and neurological involvement, neuropsychiatric damage, alopecia, malar rash, and avascular necrosis. Since organ damage has become more and more critical in SLE management, the feasibility of predicting the accumulation of organ damage has gained interest. The associations discovered in our study indicated that anti-RibP antibodies may be effective not only in the prediction of organ involvement but also in the accumulation of neuropsychiatric damage.

Anti-RibP antibody is a specific autoantibody of SLE [20] and has been reported to be associated with NPSLE [7, 21, 22] and hepatitis [23]. Anti-RibP antibodies bind to the key components of the 60S ribosomal subunit [24]. The immunoassays target the three RibP antigens (P0, P1, P2) and (or) the C-terminal 22 amino acid peptide (C22, key epitope on P0, P1, P2) [25]. According to an international meta-analysis involving > 6752 patients, this autoantibody was associated with CNS involvement, depression, and psychosis [23]. However, some studies demonstrated that anti-RibP antibodies had low sensitivity (26%) and specificity (80%) for NPSLE [26]. Our study confirmed the association between anti-RibP antibodies and baseline neurological involvement.

Although it is well accepted that anti-RibP antibodies are associated with neurological involvements, much of this information was derived from cross-sectional studies, and

Table 3 Univariable and multivariable cox regression model of associations between anti-RibP antibodies and organ damage accrual

	Neuro-psychiatric	Cognitive impairment	Seizures (therapy > 6 m)	Cerebral vascular	Cranial/peripheral neuropathy	Renal	Measured GFR < 50%	Proteinuria (24h) ≥ 3.5 g	Pulmonary fibrosis	Cardiovascular	Avascular necrosis
Univariable											
Anti-RibP	5.1(3.6-7.3)	5.1(3.0-8.8)	1.8(0.9-3.9)	2.4(1.5-4.0)	2.2(1.0-4.8)	1.2(0.8-1.8)	1.0(0.5-2.2)	1.1(0.7-1.9)	2.1(0.6-6.8)	0.3(0.0-3.0)	1.7(1.2-2.3)
APL	1.8(1.3-2.7)	1.6(1.0-2.6)	2.1(1.1-4.0)	2.3(1.2-3.9)	2.4(1.2-4.9)	0.8(0.5-1.2)	1.1(0.5-2.2)	0.6(0.4-1.1)	1.3(0.4-4.3)	2.4(1.1-5.1)	1.0(0.7-1.4)
age	1.0(0.9-1.0)	1.0(0.9-1.0)	0.9(0.8-1.0)	1.0(0.9-1.0)	1.0(0.9-1.0)	1.0(0.9-1.0)	1.0(0.9-1.0)	1.0(1.0-1.1)	1.0(0.9-1.0)	1.0(1.0-1.1)	1.0(0.9-1.0)
sex	0.6(0.3-1.2)	0.5(0.2-1.0)	1.0(0.2-4.2)	0.6(0.3-1.5)	0.6(0.2-1.9)	0.5(0.3-0.8)	0.2(0.1-0.6)	0.2(0.1-0.6)	0.5(0.2-0.9)	0.7(0.2-3.1)	1.1(0.5-2.3)
Baseline SDI > 0	1.5(1.3-1.8)	1.6(1.3-1.9)	2.0(1.6-2.5)	1.2(1.1-1.7)	1.4(1.1-2.1)	1.7(1.5-2.0)	1.8(1.5-2.4)	1.8(1.6-2.1)	1.6(1.1-2.5)	2.5(2.0-3.3)	2.1(2.0-2.4)
Multivariable											
Anti-RibP	3.8(2.7-5.7)	5.3(3.2-9.0)	1.9(1.0-3.7)	2.6(1.6-4.2)	2.0(1.0-4.1)	1.3(0.9-2.0)	1.2(0.6-2.4)	1.4(0.9-2.2)	2.2(0.7-7.0)	0.4(0.1-1.2)	1.8(1.3-2.5)
APL	1.8(1.2-2.6)	1.5(0.9-2.5)	2.0(1.0-4.0)	2.6(1.6-4.1)	2.4(1.2-4.9)	0.8(0.5-1.3)	1.2(0.6-2.5)	0.6(0.4-1.1)	1.2(0.4-4.2)	2.8(1.3-6.2)	1.0(0.7-1.4)
age	1.0(0.9-1.0)	1.0(1.0-1.1)	0.9(0.8-1.0)	0.9(0.9-1.0)	0.9(0.9-1.0)	0.9(0.9-1.0)	1.0(1.0-1.1)	0.9(0.8-0.9)	1.1(1.0-1.1)	1.0(0.9-1.1)	0.9(0.8-1.0)
sex	0.6(0.3-1.2)	0.5(0.2-0.9)	1.1(0.3-4.5)	0.7(0.3-1.6)	0.6(0.2-2.0)	0.5(0.3-0.9)	0.3(0.1-0.6)	0.5(0.3-1.0)	0.5(0.1-4.3)	1.1(0.2-5.0)	1.2(0.6-2.5)
Baseline SDI > 0	1.6(1.4-1.9)	1.7(1.4-2.0)	2.2(1.8-2.8)	1.9(1.6-2.3)	2.0(1.6-2.6)	1.9(1.6-2.2)	1.9(1.5-2.4)	2.0(1.7-2.3)	1.6(1.0-2.4)	2.5(2.0-3.3)	2.3(2.1-2.6)

Bold: *P* < 0.05

Fig. 2 Comparison of cumulative rates of not accumulating neuropsychiatric damage in anti-RibP antibody–positive and anti-RibP antibody–negative patients

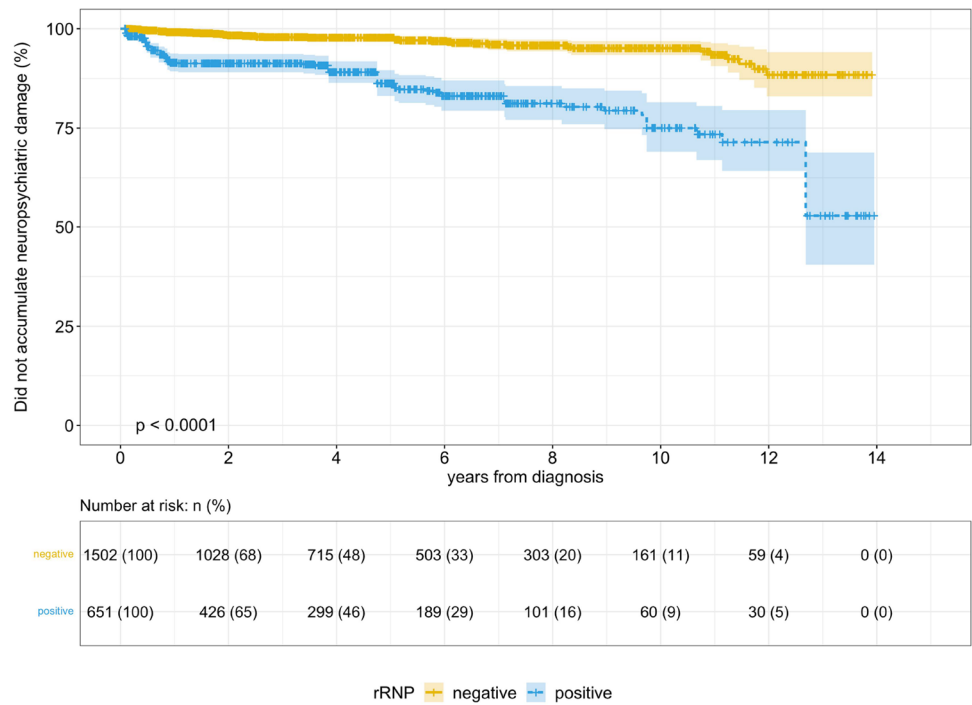
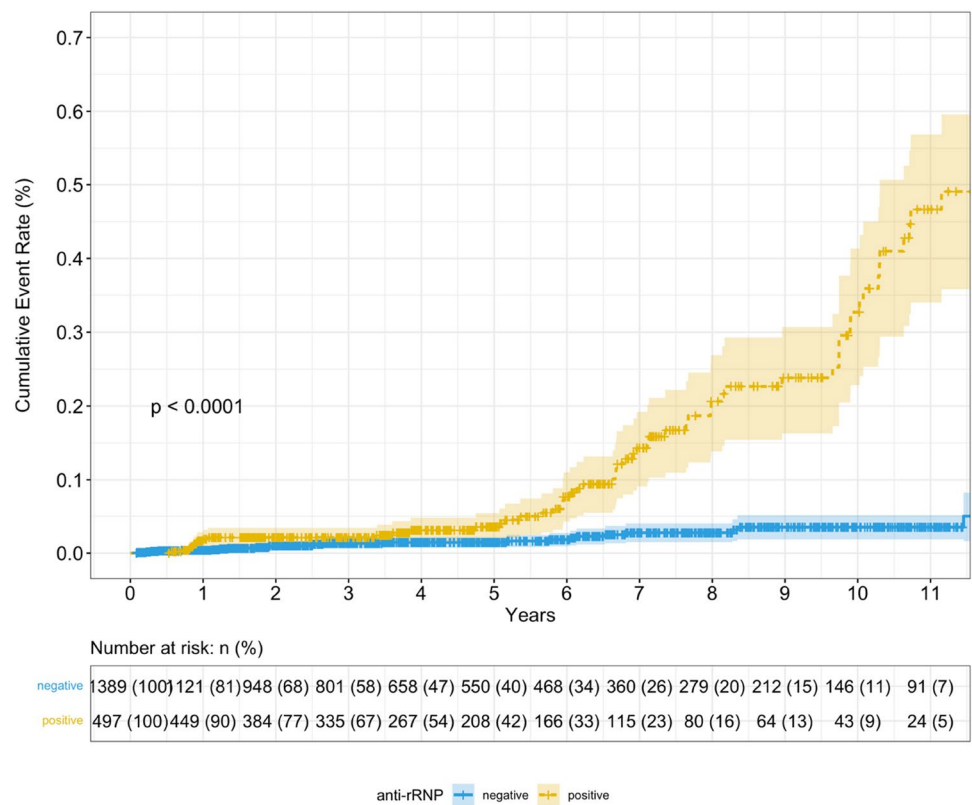


Fig. 3 Cumulative probability of new-onset neural involvement in anti-RibP antibodies positive patients



few of them focus on its prediction value on the accumulation of organ damage during follow-up [27]. Hanly et al. clarified that anti-RibP antibodies were associated with neurological involvements that occurred around the time of

diagnosis [28]. Milena Mimica et al. [29] identified that the presence of anti-nucleosome antibodies could predict neural damage accrual, but anti-RibP antibodies cannot. Older age, higher disease activity, positive anti-Ro/SSA antibody, and

positive aPL antibodies at baseline have also been reported to be associated with the development of neuropsychiatric damage [30–32]. To our best knowledge, the present study is the first to indicate the predictive value of anti-RibP antibodies on neuropsychiatric damage accrual and avascular necrosis (Table 3). What is more, we identified the cumulative probability of new-onset neurological involvement in patients with positive anti-RibP antibodies and negative neural symptoms at baseline. As the largest registry cohort study in China, CSTAR has already disclosed the features of SLE patients in China [33]. Our study might draw attention to the importance of optimizing interventions in patients with positive anti-RibP antibodies to prevent the accrual of neuropsychiatric damage.

Previous studies have provided theoretical evidence of the pathological properties anti-RibP antibodies may play in the accumulation of neuropsychiatric damage [34–36]. Anti-RibP antibodies have been reported to bind to the antigen on the neural cell membrane in the limbic system, hippocampus, and cingulate cortex [34, 35]. In murine models, anti-RibP antibodies can localize in olfactory piriform brain regions and give rise to depression-like behavior [36]. What is more, it can alter the blood-brain barrier and evoke inflammatory responses [9, 37]. However, few studies considered the fluctuation of anti-RibP antibodies, which may lead to a controversial value of anti-RibP antibodies for neuropsychiatric damage accumulation. Further studies are needed to clarify the role of anti-RibP antibodies in NPSLE pathogenesis.

Nevertheless, our study has some limitations. Our analysis did not clarify the exact pathological properties that enable anti-RibP antibodies to cause neuropsychiatric damage. Secondly, the cox analysis did not consider the fluctuation of anti-RibP antibodies. What is more, we lack data on therapeutic factors which may influence damage progression. International cohorts and further investigation into the pathological role of anti-RibP antibodies are needed.

Conclusion

In conclusion, our data demonstrated the association between anti-RibP antibodies and clinical manifestations, as well as the accumulation of organ damage. We suggest that more attention should be paid on the management of anti-RibP antibody-positive patients to predict the occurrence of organ involvements and even the accumulation of organ damage.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Yufang Ding, Jiuliang Zhao, and Mengtao Li. The first draft of the manuscript was written by Yufang Ding, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material Yes.

Code availability Yes.

Declarations

Ethics approval This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital (Approval number, S-197). Informed consent was obtained.

Disclosures None.

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