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Concomitant Sjögren's disease in patients with NMOSD: impacts on neurologic disease severity and recurrence

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Abstract

Background We aimed to characterize the phenotype of neuromyelitis optica spectrum disorder (NMOSD) in the presence and absence of Sjogren's disease (SjD) and to develop a predictive nomogram to evaluate the risk of coexisting SjD within a single tertiary-center cohort of NMOSD patients.

Methods Paraclinical and clinical features of patients with SjD were compared between NMOSD patients with SjD and those without SjD. Zstats v1.0 was utilized to randomly allocate participants into a derivation group (108 patients) and a validation group (47 patients) at a ratio of 7:3. Logistic regression analysis was used to assess the effectiveness of our predictive model, and a nomogram was created to illustrate the findings.

Results A total of 155 NMOSD patients who were serologically positive for AQP4-IgG were cross-sectionally recruited (70 NMOSD patients with SjD [45.16%] and 85 NMOSD patients without SjD [54.84%]). Independent predictors of coexisting SjD were age upon recruitment ($P=0.002$); Expanded Disability Status Scale (EDSS) score ($P=0.023$); blood white blood cell (WBC) count ($P=0.049$); and rheumatoid factor (RF) ($P=0.049$), anti-SSA (Ro), and anti-SSB (La) antibody positivity ($P<0.001$; $P=0.012$). The nomogram had an area under the receiver operating characteristic (ROC) curve (AUC) (95% confidence interval [CI]) of 0.95 (0.89, 1.00) in the derivation cohort and 0.91 (0.79, 1.00) in the validation cohort. Survival curve analysis revealed that the EDSS score in the NMOSD patients with SjD was associated with clinical relapse, and these patients reached an EDSS score of 4.0 earlier than those without SjD.

Conclusion NMOSD patients with SjD manifested more severe disease at attack and relapsed earlier than those without SjD. The nomogram established by combining age upon recruitment; EDSS score; blood WBC count; and RF, anti-SSA (Ro), and anti-SSB (La) antibody levels can significantly predict the risk of NMOSD combined with SjD.

Keywords Neuromyelitis optica spectrum disorder, AQP4-IgG, Sjogren's disease, Prognosis, Nomogram

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD), a rare autoimmune disease, can cause multifocal central nervous system (CNS) inflammation and primarily affects the optic nerves and spinal cord, typically resulting in visual loss and paralysis [1]. NMOSD can be classified as an astrocytopathic autoimmune disease of the CNS caused by detrimental antibodies specifically directed at the aquaporin-4 (AQP4) protein located on astrocyte foot processes [2]. Astrocytes play crucial roles in the creation and maintenance of the blood–brain barrier (BBB). The AQP4-IgG antibodies exhibit high specificity and affinity for the AQP4 antigenic site, triggering the complement cascade and intensifying inflammatory responses. This process leads to disruption of the BBB, astrocyte injury or dysfunction, subsequent demyelination, and ultimately, the onset and progression of NMOSD [3]. NMOSD shows a heightened propensity for concurrent presence with Sjogren's disease (SjD) and systemic lupus erythematosus (SLE) in comparison with other autoimmune diseases [4]. Among a cohort of AQP4-IgG seropositive NMOSD patients, 35.1% manifested autoimmune comorbidities, whereas 51.4% tested positive for systemic autoantibodies, such as anti-SSA (Ro) antibody, anti-SSB (La) antibody, and antinuclear (ANA) antibody [5]. Anti-SSA (Ro) antibodies are frequently identified in various connective tissue diseases, including conditions such as SjD, SLE, and vasculitis [6, 7]. Furthermore, the presence of anti-SSA (Ro) antibodies is often closely associated with longitudinally extensive transverse myelitis (LETM) lesions, and their coexistence is frequently observed in patients with AQP4-IgG seropositive NMOSD [8, 9]. It was previously reported that NMOSD patients have a fivefold greater risk of developing SjD than does the general population [10]. The coexistence of SjD was associated with poor outcomes in terms of increased morbidity for patients and increased health care burden. Previous cohort studies revealed that the serum levels of immunoglobulins (IgA, IgM, and IgG) were markedly greater in patients with NMOSD with SjD than in patients with NMOSD without SjD [11]. However, effective predictors for distinguishing NMOSD patients with or without SjD have not been defined. In our current study, we aimed to categorize NMOSD patients into two distinct groups—those with SjD and those without—and to conduct a comparative analysis of their clinical features. The characteristics of this subset of NMOSD patients are currently under evaluation, and an understanding of these characteristics might be necessary for better patient stratification, tailored therapy and follow-up. We used logistic regression analysis to predict the likelihood of SjD coexistence among NMOSD patients. Furthermore, we developed a predictive nomogram that estimates the risk of SjD coexistence in NMOSD patients.

Methods

Patient eligibility and study design

Patients who were diagnosed with NMOSD between 10/2013 and 10/2023 in the Department of Neurology at Huashan Hospital of Fudan University were included in this study. Data on the clinical features of treatment-naïve patients were retrospectively collected at baseline. The inclusion criteria for the subjects included in the cohort were as follows: (1) were diagnosed with NMOSD on the basis of the revised 2015 Wingerchuk criteria [12] or 2007 Wingerchuk diagnostic criteria [13] and were serologically positive for AQP4-IgG; (2) experienced an acute attack period (defined as new or worsening neurological deficits lasting for at least 24 h and occurring > 30 days after the previous attack); (3) had symptoms that were not attributable to confounding clinical factors, such as fever, infection, injury, disability, changes in mood, or adverse reactions to medications; and (4) were male or female and aged ≥ 18 years. The diagnosis of SjD was reassessed for each patient and was based on the diagnostic criteria of the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) [14] or 2012 ACR classification [15].

Evaluation of NMOSD disease activity

The Expanded Disability Status Scale (EDSS) was applied as a predefined standardized evaluation scale to assess demographic and diagnostic data and attack-related clinical features by neurologists (HY, XZ, and XJC) [16]. The symptom severity was rated as mild disability (EDSS score of 0–3.5) or moderate/severe disability (EDSS score of 4.0–9.5) [17]. Neurologic function, including visual acuity and disability assessments, was assessed at the time of attack and at the 1-, 3- and 6-month follow-up visits.

AQP4-IgG assay

AQP4-IgG titers were measured via a cell-based assay (CBA) commercial kit (Siemens Medical Diagnosis Co., Ltd.) according to the manufacturer's instructions. Onconeuronal antibody titers were measured with a diagnostic kit provided by Ravo Diagnostics GmbH (Freiburg, Germany). Patients with titers of the above antibodies ≥ 1:10 were considered positive.

Statistical and graphical analysis

Categorical data were analyzed for disparities between groups via Fisher's exact test. For continuous variables, the Mann–Whitney test was used to assess group

differences. Unordered multiclass variables were compared via the Kruskal–Wallis test. The Kaplan–Meier method was used to analyze the elapsed time from the onset of NMOSD to an EDSS score of 4.0 and to track the time to relapse, with survival curves compared via a log-rank test. These analyses were conducted with GraphPad Prism Version 10.2.0.

Zstats v1.0 software, which is based on the R programming language, was used to randomly allocate participants into a derivation group (108 patients) and a validation group (47 patients) at a ratio of 7:3. Patients were categorized into two cohorts on the basis of the presence or absence of SjD. Logistic regression analysis was then conducted to identify significant factors differentiating NMOSD patients with SjD from NMOSD patients without SjD. A nomogram was subsequently constructed from the selected model to provide a visual representation of the predictive outcomes. The predictive performance of the model was evaluated via receiver operating characteristic (ROC) curve, calibration plot, and decision curve analysis (DCA) to assess model discriminatory power, calibration accuracy, and clinical utility, respectively.

Results

Older age and higher EDSS scores at baseline in patients with NMOSD with SjD

A total of 155 NMOSD patients were enrolled during their attack period at our site. The algorithm for recruitment is shown in Fig. 1. The baseline demographic and clinical features of these NMOSD patients are shown in Table 1. Patients with NMOSD with SjD (indicated as NMOSD with SjD) accounted for 45.16% (70/155) of the study sample, whereas patients with NMOSD without SjD (indicated as NMOSD without SjD) accounted for 54.84% (85/155) of the study sample. The sex ratio and disease course were not significantly different between the groups (Table 1). Analysis of other baseline characteristics of patients with SjD revealed a significantly greater age at onset ($P<0.001$) and upon recruitment ($P<0.001$) in patients with NMOSD with SjD than in patients with NMOSD without SjD. The EDSS score was significantly greater in the NMOSD with SjD group [6 (3,6.5), median (IQR)] than in the NMOSD without SjD group [3 (3,6), median (IQR)] ($P<0.001$). The detailed characterization is shown in detail in Table 1. The immunosuppressant induction treatments used were generally similar between patients with NMOSD with SjD and those without SjD (Table 1).

Differential inflammatory and immune markers

Laboratory examinations revealed significantly lower blood white blood cell (WBC) counts ($P=0.004$) and higher erythrocyte sedimentation rate (ESR) ($P=0.002$) and rheumatoid factor (RF) levels ($P<0.001$) in NMOSD patients with SjD than in NMOSD patients without SjD. Furthermore, a comparison of laboratory parameters revealed a significantly greater positivity rate (100% *vs.* 56.76%) for anti-ANA antibodies ($P<0.001$), anti-SSA (Ro) antibodies (90% *vs.* 30.67%) ($P<0.001$), and anti-SSB (La) antibodies (27.14% *vs.* 5.33%) ($P<0.001$) in patients with SjD. Other laboratory parameters, such as serum IgG, serum component 3 (C3), serum component 4 (C4), and total blood B lymphocyte percentage, were also measured. Moreover, analysis of cerebrospinal fluid (CSF) revealed no significant differences in the total WBC count or total protein level in the CSF between NMOSD patients with SjD and those without SjD. The laboratory features are listed in Table 2.

NMOSD without SjD tends to present with optic neuritis combined with myelitis

In the evaluation of clinical attack modes among NMOSD patients, optic neuritis occurred in 25.71% of the NMOSD with SjD group and 21.18% of the NMOSD without SjD group (Fig. 3a), with no significant difference between groups ($P=0.568$). Myelitis was present in 48.57% of the patients in the NMOSD with SjD group and 42.35% of patients in the NMOSD without SjD group (Fig. 3a), but the difference was not statistically significant ($P=0.517$). However, the coexistence of optic neuritis and myelitis was significantly more common in the NMOSD without SjD group ($P=0.003$). All participants underwent noncontrast magnetic resonance imaging (MRI) at recruitment to identify the site of the lesions (Table 3). Notably, area postrema involvement as detected via MRI was more common in the NMOSD patients with SjD than in the NMOSD patients without SjD ($P=0.090$), which is consistent with the percentage of patients with area postrema syndrome (NMOSD with SjD: 18.57% *vs.* NMOSD without SjD: 10.59%). However, other areas of lesion involvement were not significantly different between the groups (Table 3).

Establishment of a predictive nomogram for SjD coexisting with NMOSD

Independent predictors of the coexistence of SjD in patients with NMOSD included age upon recruitment (odds ratio [OR] = 1.05 [95% confidence interval {CI}: 1.02–1.08], $P=0.002$); EDSS score (OR = 1.26 [95% CI: 1.03–1.55], $P=0.023$); blood WBC count (OR = 0.88 [95% CI: 0.77–0.99], $P=0.049$); and RF (OR = 1.33 [95% CI: 1.01–1.77], $P=0.049$), anti-SSA(Ro) antibody (OR = 21.64 [95% CI: 6.72–69.70], $P<0.001$) and anti-SSB (La) antibody (OR = 4.73 [95% CI: 1.41–15.90], $P=0.012$) levels, as shown in Table 4.

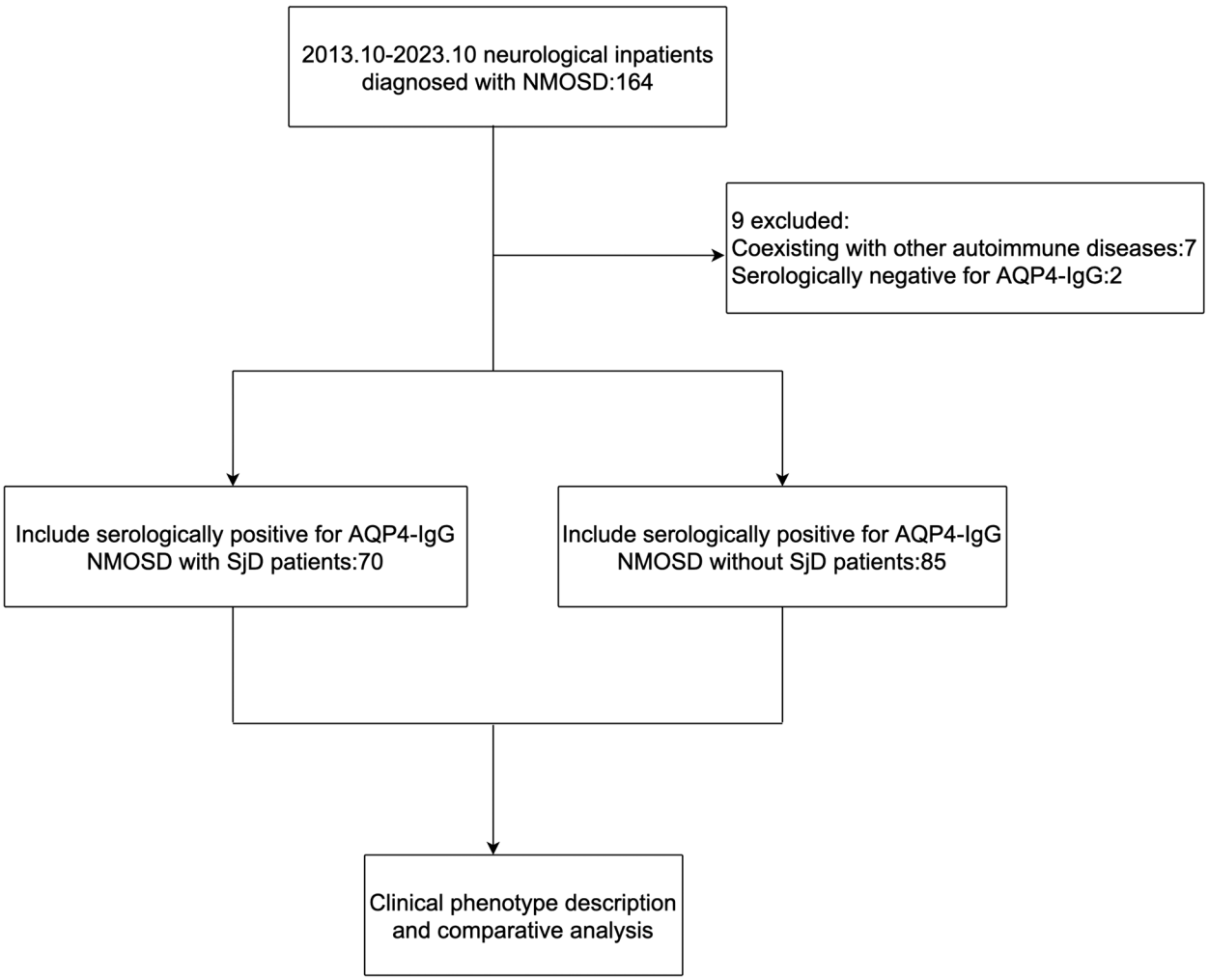

Fig. 1 Case–control study flowchart of the inclusion of serologically positive AQP4-IgG NMOSD patients. A total of 164 patients diagnosed with NMOSD from October 2013 to October 2023 were included. Among these patients, 9 were excluded because of the coexistence of other autoimmune diseases (7 patients) or because they were serologically negative for AQP4-IgG (2 patients). The remaining patients were categorized into two groups on the basis of the presence of SjD: 85 without SjD and 70 with SjD. The subsequent sections of the study involve a detailed description and comparison of the clinical phenotypes of the two groups. The flowchart was generated using Figdraw Version 2.0. NMOSD: neuromyelitis optica spectrum disorder; SjD: Sjogren's disease

These predictors were included in a nomogram, which enables calculation of the total points for each NMOSD patient, resulting in predicted probabilities for the coexistence of SjD in NMOSD patients (Fig. 4a). The model exhibited high discriminatory power, with an area under the ROC curve (AUC) of 0.95 (95% CI: 0.89–1.00; Fig. 2b) in the derivation cohort and an AUC of 0.91 (95% CI: 0.79–1.00; Fig. 2c) in the internal validation cohort. The observed percentages of response corresponded well with the predicted probabilities (Hosmer–Lemeshow: $P=0.666$, Fig. 3a) and calibration ability (Hosmer–Lemeshow: $P=0.338$, Fig. 3b) in the internal validation cohort. DCA of both the derivation cohort (Fig. 3c) and the validation cohort (Fig. 3d) revealed that the model line was almost above the treatment line and that no line was within the range of values of the horizontal axis, which is indicative of the potential clinical utility of this model.

Kaplan–Meier survival curves for EDSS score and relapse in NMOSD patients with and without SjD

To investigate the influence of coexisting SjD on EDSS score and relapse in NMOSD patients, we analyzed the follow-up data using Kaplan–Meier survival curves. NMOSD relapse was defined as new-onset, progressive, or recurrent neurological symptoms caused by NMOSD that last longer than 24 h and resulted in an increase in

Table 1 Baseline demographic and clinical characteristics of patients with NMOSD categorized based on the presence or absence of SjD

	NMOSD with SjD	NMOSD without SjD	*P* value
N total	70	85	-
N (%)	45.16%	54.84%	-
Female, N (%)	63 (90%)	74 (87.06%)	0.623
Age upon recruitment (years), median (IQR)	50.5 (37,56)	37 (28,50.5)	< 0.001
Age at disease onset (years), median (IQR)	47.5 (34,55)	33 (27,45)	< 0.001
Disease duration (months), median (IQR)	7.5 (1,48)	5 (1,38.25)	0.613
EDSS upon attack, median (IQR)	6 (3,6.5)	3 (3,6)	< 0.001
Serum positivity for AQP4-IgG (CBA)	70 (100%)	85 (100%)	-
Immunosuppressant induction treatment, N (%)			
Glucocorticoids	61 (87.14%)	59 (69.41%)	
Rituximab	20 (28.57%)	23 (27.06%)	
Cyclophosphamide	10 (14.29%)	1 (1.18%)	
PLEX	2 (2.86%)	18 (21.18%)	
MMF	10 (14.29%)	12 (14.12%)	
AZA	3 (4.29%)	2 (2.35%)	0.069
Inerizumab	1 (1.43%)	4 (4.71%)	
Sarterizumab	1 (1.43%)	1 (1.18%)	
IVIG	7 (10.00%)	7 (8.24%)	
Cyclosporinea	1 (1.43%)	0 (0.00%)	

PLEX plasma exchange, *MMF* mycophenolate mofetil, *AZA* azathioprine, *IVIG* intravenous immunoglobulin

Table 2 Baseline laboratory findings for immunological parameters for patients with NMOSD categorized based on the presence or absence of SjD

	NMOSD with SjD	NMOSD without SjD	*P* value
Blood WBC (×10^9/L), median (IQR)	6.78 (5.23,9.68)	9.37 (6.33,11.31)	0.004
IgG (g/L), median (IQR)	12.20 (8.05,14.60)	9.47 (8.13,12.60)	0.287
C3 (g/L), median (IQR)	0.91 (0.79,1.03)	0.92 (0.80,1.05)	0.899
C4 (g/L), median (IQR)	0.17 (0.12,0.24)	0.18(0.14,0.23)	0.549
ESR (mm/h), median (IQR)	14 (8,28)	5 (2,19)	0.002
RF (IU/mL), median (IQR)	10.55 (9.75,12.53)	9.38 (9.13,10.60)	< 0.001
Total B cell percentage, median (IQR)	15.26 (9.14,20.70)	15.68 (9.47,21.96)	0.835
CSF total WBC (×10^6/L), median (IQR)	3 (1,6.25)	4 (2,11.50)	0.258
CSF total protein (mg/L), median (IQR)	471.0 (350.0,631.0)	471.5 (357.3,589.5)	0.825
Oligoclonal bands in CSF negative ratio	42 available	26 available	
	35 (83.33%)	23 (88.46%)	0.730
ENA profile	70 available	74 available	
ANA postivity	70 (100%)	42 (56.76%)	< 0.001
SSA (Ro) postivity	63 (90%)	23 (30.67%)	< 0.001
SSB (La) postivity	19 (27.14%)	4 (5.33%)	< 0.001

the EDSS score of at least 0.5 points, an increase in two functional system (FS) scale scores of at least 1 point, an increase in one FS scale score of at least 2 points, or new lesions on MRI [18, 19]. The median interval to NMOSD relapse was 19 months in the NMOSD with SjD group and 34 months in the NMOSD without SjD group ($P=0.002$) (Fig. 4a). Limited walking without assistance is considered an EDSS score of 4.0 [20]. The median times to reach an EDSS score of 4.0 in the NMOSD with SjD group and the NMOSD without SjD group were 24 months and 36 months, respectively ($P=0.001$, Fig. 4b). Therefore, these data suggest that the concurrent

Table 3 Attack mode and MRI findings for patients with NMOSD stratified by the coexistence with or without SjD

	NMOSD with SjD	NMOSD without SjD	*P* value
Clinical attack mode	70 available	85 available	
Optic neuritis	18 /52 (25.71%)	18/67 (21.18%)	0.568
Myelitis	34 /36 (48.57%)	36/49 (42.35%)	0.517
Area postrema syndrome	13/57 (18.57%)	9/76 (10.59%)	0.172
Optic neuritis + myelitis	5/65 (7.14%)	22/63 (25.88%)	0.003
Clinical site of the lesion at recruitment	70 available	85 available	
Optic nerve	3/67 (4.29%)	6/79 (6.98%)	0.514
Cervical	13/57 (18.57%)	16/69 (18.61%)	> 0.999
Thoracic	11/59 (15.71%)	15/70 (17.44%)	0.831
Cervicothoracic	17/53 (24.29%)	12/73 (13.95%)	0.147
Lumbar	1/69 (1.43%)	1/84 (1.16%)	> 0.999
Area postrema	3/67 (4.29%)	0/85 (0%)	0.090
Brainstem	5/65 (7.14%)	3/82 (3.49%)	0.469
Brainstem + cervical	1/69 (1.43%)	5/80 (5.81%)	0.223
Cerebral	5/65 (7.14%)	9/76 (10.47%)	0.578
Absent	11/59 (15.71%)	19/66 (22.09%)	0.316

Table 4 Uni-and multivariate regression analyses for significant variables

Variables	Univariate OR [95% CI]	Univariate *P* value	Multivariate OR [95% CI]	Multivariate *P* value
Sex	0.82 (0.27—2.43)	0.714		
Age upon recruitment	1.05 (1.02—1.08)	0.002	1.06 (0.96—1.17)	0.214
Disease duration (months)	1.00 (0.99—1.00)	0.578		
EDSS	1.26 (1.03—1.55)	0.023	1.27 (0.70—2.28)	0.434
Blood WBC (×10^9/L)	0.88 (0.77—0.99)	0.049	0.72 (0.46—1.11)	0.137
ESR (mm/h)	1.01 (0.98—1.04)	0.399		
RF (IU/mL)	1.33 (1.01—1.77)	0.049	1.94 (0.95—3.93)	0.068
C3 (g/L)	0.64 (0.05—8.04)	0.727		
C4 (g/L)	0.34 (0.01—9.46)	0.529		
Serum IgG (g/L)	0.98 (0.86—1.12)	0.773		
Total B cell percent	0.94 (0.88—1.01)	0.085		
ANA positivity	179,455,023.61 (0.00—Inf)	0.988		
SSA (Ro) positivity	21.64 (6.72—69.70)	< 0.001	14.23 (1.33—151.96)	0.028
SSB (La) positivity	4.73 (1.41—15.90)	0.012	29,550,667.36 (0.00—Inf)	0.995
CSF total WBC (*10^6/L)	0.97 (0.92—1.01)	0.145		
CSF total protein (mg/L)	1.00 (1.00—1.00)	0.895		

presence of SjD exacerbates disease severity, as measured by the EDSS, and increases the frequency of relapses in patients with NMOSD.

Discussion

Our research on a retrospective longitudinal cohort indicates that NMOSD patients with coexisting SjD display a unique clinical profile in comparison to those without SjD. The predictive model may provide an approach to integrate predictive factors into clinical decision-making in clinical practice.

Our cohort analysis revealed a female-to-male ratio of approximately 9:1, which is consistent with previous research [21]. The age at disease onset in the NMOSD with SjD group was greater than that in the NMOSD without SjD group [22]. A previous study found that the incidence increased with age, peaking at 55–64 years in females and 65–74 years in males and then decreasing thereafter. Sex and age influence the risk of NMOSD,

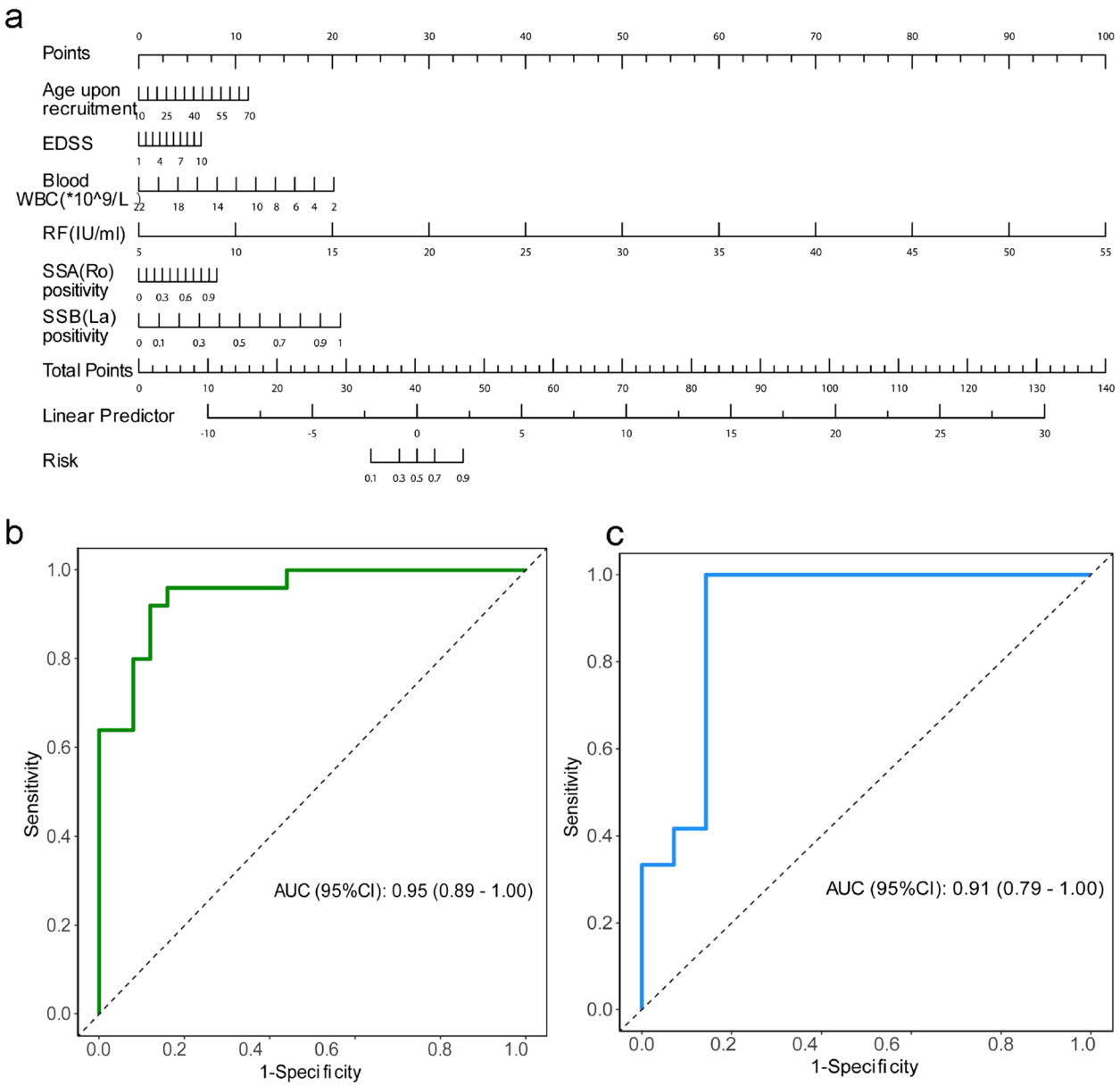

Fig. 2 ROC-AUC of the nomogram. **a** Nomogram to estimate the risk of coexisting SjD in the 155 included NMOSD patients. To use this nomogram, locate the position of each variable on the corresponding axis, draw a line from that point to the point axis to represent the number of points, add up the points from all the variables, and draw a line from that total points value to the risk axis to determine the risk of coexisting SjD in NMOSD patients. **b** ROC curve analysis of the derivation cohort. The AUC was 0.95, with a 95% CI ranging from 0.89 to 1.00, indicating the excellent discriminatory ability of the test. **c** ROC curve analysis of the validation cohort. The AUC was 0.91, with a 95% CI ranging from 0.79 to 1.00, indicating the excellent discriminatory ability of the test. The above analysis was performed via Zstats v1.0 software (www.zstats.net), which is based on the R programming language. ROC: receiver operating characteristic, AUC: area under the curve, CI: confidence interval, NMOSD: neuromyelitis optica spectrum disorder, SjD: Sjogren's disease

suggesting the role of genetic, hormonal and other related factors in the pathophysiology of this disease [23]. Our results indicate that the EDSS score was higher in the NMOSD with SjD group than in the NMOSD without SjD group ($P<0.001$). We observed that NMOSD patients with SjD tended to relapse earlier and have more severe disease. These findings were consistent with previous research showing that anti-SSA (Ro) antibodies could be associated with disease activity and disability severity in patients with NMOSD [24]. A previous study indicated that the incidences of xerophthalmia, xerostomia, arthritis, interstitial lung disease, and renal tubular acidosis

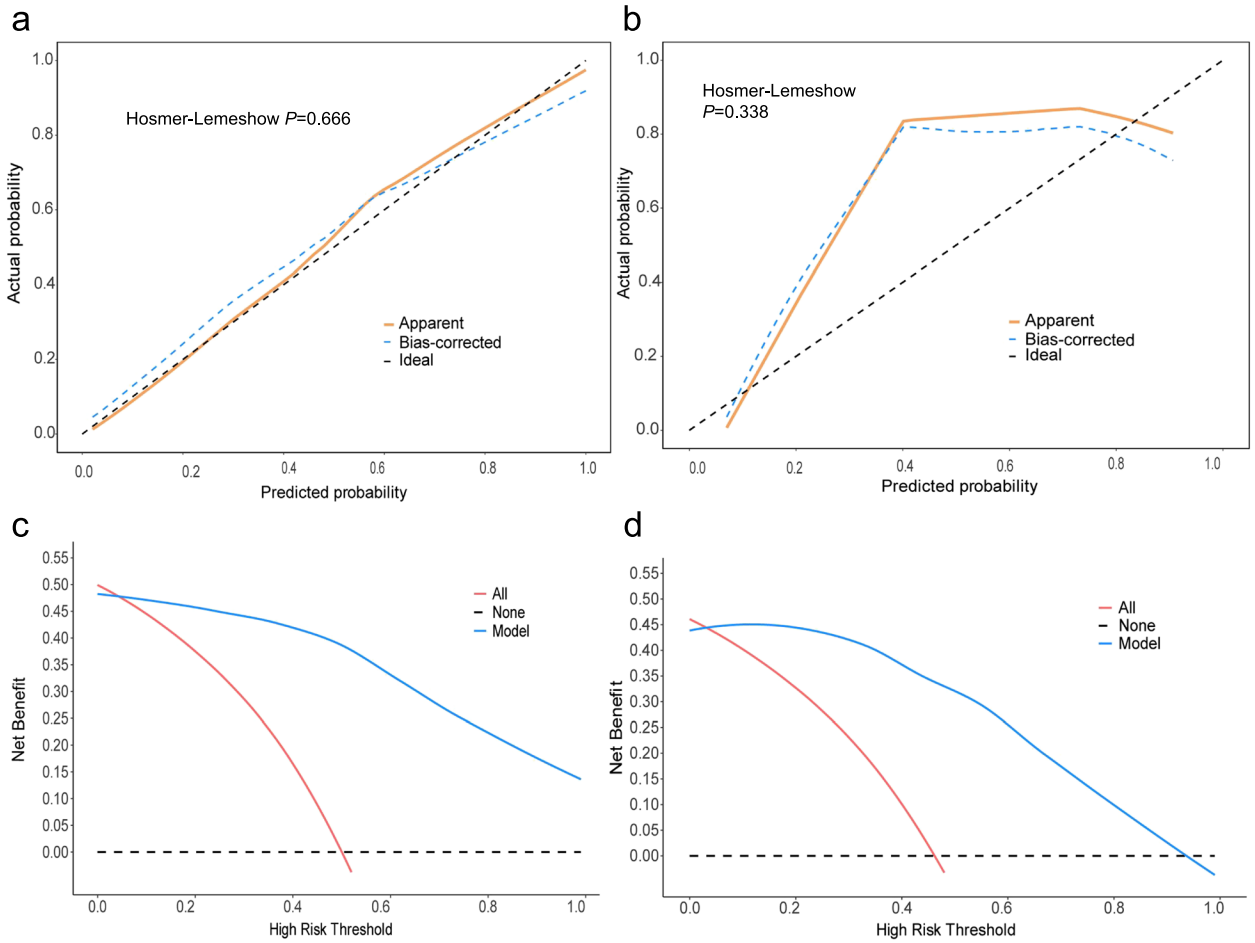

Fig. 3 Model calibration and DCA of the derivation and validation cohorts. **a** Calibration plot of the derivation cohort. The *P* value of the Hosmer–Lemeshow test was 0.666, indicating that there was no significant difference between the observed and predicted values, suggesting a well-calibrated model. **b** Calibration plot of the validation cohort. The *P* value of the Hosmer–Lemeshow test was 0.338, indicating that there was no significant difference between the observed and predicted values, suggesting a well-calibrated model. **c** DCA for the derivation cohort. **d** DCA for the validation cohort. The DCA plot helps to visualize the trade-off between the benefits and harms of implementing the model in clinical practice and can guide the decision-making process regarding the appropriate threshold for intervention. The above analysis was performed via Zstats v1.0 software (www.zstats.net), which is based on the R programming language. DCA: decision curve analysis

were significantly lower in SjD patients with NMOSD than in SjD patients without NMOSD [25]. Akaishi and colleagues reported that among AQP4-IgG seropositive NMOSD patients, 26.3% were positive for anti-SSA (Ro) antibodies [8]. The probability of anti-SSA (Ro) antibody positivity was greater in NMOSD patients than healthy controls, and analysis of our cohort revealed that 59.72% of NMOSD patients were positive for anti-SSA (Ro) antibodies, which is in agreement with the above studies. Our findings suggest that anti-SSA (Ro) antibody positivity could be a risk factor for NMOSD relapse and worse outcomes in terms of EDSS scores. The study revealed differences in the interval to reach an EDSS score of 4.0 and relapse rates between NMOSD patients with SjD and those without SjD.

Logistic regression analysis revealed that age of onset; EDSS score; WBC count; and RF, anti-SSA (Ro), and anti-SSB (La) antibody positivity were potential independent factors associated with a risk of coexisting SjD in NMOSD patients. The efficacy of these predictors is supported by our ROC curve analysis and cohort validation findings, which indicated the reliability of these factors in determining the coexistence of SjD in NMOSD patients. Furthermore, the nomogram offers a visual predictive tool that could be instrumental in guiding clinical decision-making and practices.

Compared with NMOSD patients without any autoimmune disorders, NMOSD patients with SjD may have a refractory disease course and severe physical functional impairment. Further investigation is required to

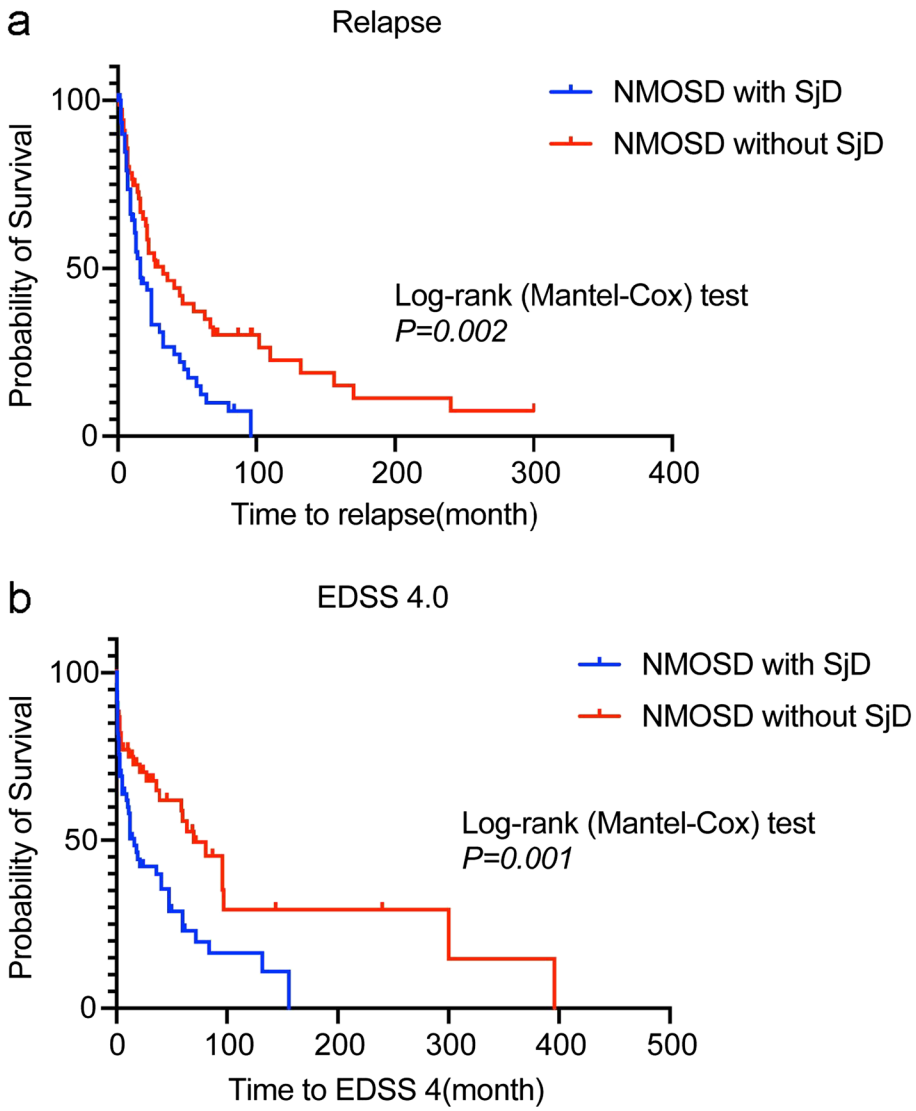

Fig. 4 **a** Kaplan–Meier survival curves indicating cumulative relapse in NMOSD patients, points with the same follow-up time, and those with SjD and a high relapse rate. **b** Kaplan–Meier survival curves and log-rank tests were used to compare the time from NMOSD onset to an EDSS score of 4.0 between NMOSD patients with SjD and those without SjD. These analyses were conducted via GraphPad Prism Version 10.2.0. EDSS: Expanded Disability Status Scale, NMOSD: neuromyelitis optica spectrum disorder, SjD: Sjogren's disease

determine whether we should administer advanced therapy for NMOSD patients with a background of systemic autoimmune diseases, such as SjD. To our knowledge, few studies have directly evaluated the optimal therapy for NMOSD patients with SjD. Previous data indicating a high risk of relapse in NMOSD patients who test positive for anti-AQP4 autoantibodies support the recommendation for immunosuppressive therapy. Immunosuppressive therapy is recommended due to the significant association with visual impairment and the elevated risk of experiencing neurological relapses within a year of 60% [26, 27]. Currently, corticosteroid pulse therapy for early induction and the use of immunosuppressants such as cyclophosphamide and azathioprine for maintenance are recommended. Rituximab and tocilizumab have also demonstrated sustained clinical efficacy in treatment-resistant patients [28, 29]. However, long-term observational studies are needed to determine the standard management of SjD with NMOSD.

The mechanisms underlying the contribution of anti-SSA (Ro) antibodies to the pathology of NMOSD are not fully understood. Various potential immunological processes have been hypothesized: the anti-SSA (Ro) antibody may attach to the SSA antigen present in vascular

endothelial tissues, potentially leading to increased BBB permeability [9, 30]. The spectrum of neurological manifestations in SjD encompasses heterogeneous clinical signs ranging from silent abnormalities on MRI scans to more pronounced conditions, such as meningitis, myelopathy, nerve damage in the head, combined sensory and motor neuropathies, or multiple mononeuritis [31, 32]. Vasculitis and autoimmune demyelination have been revealed as potential mechanisms underlying this pathological process [33]. NMOSD has been recognized, and standardized diagnostic procedures and treatment guidelines have been formulated and updated. However, the diagnosis of coexisting SjD might be neglected, and there is no standardized treatment plan for neurological manifestations in patients with SjD. Identification of the coexistence of NMOSD and SjD at an early stage may increase our ability to predict patient outcomes and better guide patient follow-up. Further foundational research is needed to explore the mechanisms involved, facilitating more precise and personalized therapeutic approaches for affected individuals.

The present study is subject to several limitations: Firstly, it is a retrospective study with a relatively small sample size, thus the conclusion requires further confirmation using a larger sample. Secondly, incomplete medical records and unavoidable missing data resulted in the exclusion of certain variables. For instance, 37 patients underwent a biopsy of the minor salivary glands, with 28 patients in the NMOSD with SjD group and 9 patients in the NMOSD without SjD group. Thirdly, due to the retrospective nature of the study, which collected case information from 2013 to 2023, the 2012 Sjögren's disease classification criteria are less applicable in the current context.

Conclusion

Patients with NMOSD coexisting with SjD present distinct clinical features. The presence of SjD in NMOSD patients is associated with increased disability and a poorer prognosis. A predictive nomogram that integrates factors such as the age at disease onset; EDSS score; blood WBC count; and positivity for RF, anti-SSA (Ro) and anti-SSB (La) antibodies can precisely predict the risk of SjD in NMOSD patients, which may provide guidance in therapeutic selection for NMOSD patients with a background of systemic autoimmune disease.

Supplementary InformationSupplementary Fig.1 Correlations between age at recruitment and EDSS score. The figure illustrates the relationship between age upon recruitment and the EDSS score in 155 patients, including serum-positive AQP4-IgG NMOSD patients. Spearman analysis was conducted via GraphPad Prism Version 10.2.0. EDSS: Expanded Disability Status Scale, NMOSD: neuromyelitis optica spectrum disorder.Supplementary Fig.2 Attack mode distribution in NMOSD patients with and without SjD. a Percentage of NMOSD patients with or without SjD experiencing different attack modes, including optic neuritis (ON), myelitis, area postrema syndrome (APS) and ON combined with myelitis. b Attack modes were analyzed for disparities between groups via Fisher's exact test (conducted via GraphPad Prism Version 10.2.0.).Supplementary Fig.3 Lesion distribution in NMOSD patients with and without SjD. a Percentage of NMOSD patients with and without SjD exhibiting lesions in various regions. b Lesion distributions were analyzed for disparities between groups via Fisher's exact test (conducted via GraphPad Prism Version 10.2.0.).Supplementary Fig.4 Comparative analysis of differential inflammatory and immune markers in NMOSD patients with and without SjD. a Baseline laboratory findings for immunological parameters detected in the blood of the 155 included serologically positive AQP4-IgG NMOSD patients (85 without SjD and 70 with SjD). b Baseline laboratory findings for immunological parameters detected in the CSF of the 155 included serologically positive AQP4-IgG NMOSD patients (85 without SjD and 70 with SjD). NMOSD: neuromyelitis optica spectrum disorder, SjD: Sjogren's disease, WBC: white blood cell, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, C3: complement 3, C4: complement 4, CSF: cerebrospinal fluid. The above analyses were conducted via GraphPad Prism Version 10.2.0.

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Authors' contributions

Conception and design of the study: XJC, MRL; major role in acquisition and analysis of data: WQW, BD, HLL, XNL, HY, XZ; drafting a significant portion of the manuscript or figures: WQW, BD, HLL; revised the details of the manuscript: WQW, WBY. All the authors read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Huashan Hospital, Fudan University: (2023) Trial No. (529).

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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