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Research Paper

Exploring core symptoms and symptom clusters among patients with neuromyelitis optica spectrum disorder: A network analysis

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ABSTRACT

Objectives: To identify core symptoms and symptom clusters in patients with neuromyelitis optica spectrum disorder (NMOSD) by network analysis.
Methods: From October 10 to 30, 2023, 140 patients with NMOSD were selected to participate in this online questionnaire survey. The survey tools included a general information questionnaire and a self-made NMOSD symptoms scale, which included the prevalence, severity, and distress of 29 symptoms. Cluster analysis was used to identify symptom clusters, and network analysis was used to analyze the symptom network and node characteristics and central indicators including strength centrality (r_s), closeness centrality (r_c) and betweeness centrality (r_b) were used to identify core symptoms and symptom clusters.
Results: The most common symptom was pain (65.7%), followed by paraesthesia (65.0%), fatigue (65.0%), easy awakening (63.6%). Regarding the burden level of symptoms, pain was the most burdensome symptom, followed by paraesthesia, easy awakening, fatigue, and difficulty falling asleep. Six clusters were identified: somatosensory, motor, visual, and memory symptom clusters, bladder and rectum symptom clusters, sleep symptoms clusters, and neuropsychological symptom clusters. Fatigue ($r_s = 12.39$, $r_b = 68.00$, $r_c = 0.02$) was the most central and prominent bridge symptom, and motor symptom cluster ($r_s = 2.68$, $r_c = 0.10$) was the most central symptom cluster among the six clusters.
Conclusions: Our study demonstrated the necessity of symptom management targeting fatigue, pain, and motor symptom cluster in patients with NMOSD.

What is known?

- Patients with neuromyelitis optica spectrum disorder (NMOSD) often suffer from a variety of symptoms.
- The comprehensive symptom status and relationships between multiple symptoms in NMOSD patients remain unclear.

What is new?

- This study identified the symptom clusters and core symptoms and explore their interrelationships among symptoms in NMOSD patients.
- Pain was the most prevalent and burdensome symptom, and fatigue was the most central and prominent bridge symptom in NMOSD patients.
- Motor symptom cluster was the most central symptom cluster among six symptom clusters identified in patients with NMOSD.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare and severe central nervous system inflammatory disease [1]. The global incidence rates of NMOSD ranged from 0.07 to 10 per 100,000 population, with a pooled prevalence of 1.54 (95%*CI*: 1.13–1.96) [2]. Due to the involvement of acute episodes of optic neuritis or transverse myelitis, patients with NMOSD often suffer from a variety of symptoms, such as visual impairment, motor impairment, pain, fatigue, sleep disorders, bladder and rectum dysfunction, and psychological disorders [3,4]. Symptom distress and the burden of

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symptom management have been reported as essential factors in decreased quality of life for NMOSD patients [5,6].

Previous studies [6,7] suggest that pain was the most common symptom that NMOSD patients wanted their physician to be concerned about, which has a strong negative correlation with quality of life. Additionally, findings from Zahra et al. [4] suggested that patients with NMOSD significantly had psychological disorders such as depression, anxiety, and hostility compared to healthy controls. Overall, a high-level symptom burden of NMOSD patients has been observed in previous studies [5,6]. However, most studies focus solely on a single symptom (e.g., pain, fatigue) [7] or a specific class of symptoms (e.g., psychological disorders) [4] and ignore the comprehensive symptom status and relationships between multiple symptoms. A comprehensive understanding of symptom networks, such as core and bridge symptoms, is essential to develop and deliver effective symptom management strategies for NMOSD patients.

Symptom cluster refers to symptoms in the same individual that may co-occur as a pair of two symptoms [8]. Identifying symptom clusters is an essential approach for dimension reduction in real-world clinical practice to simplify complex symptom interactions [9]. Identifying symptom clusters of patients with NMOSD may lead to a better understanding of how symptoms interrelate and provide greater insight into clinical symptom management. Currently, exploring symptom clusters has been widely used in various populations and diseases [10–12], but limited relevant research has yet been described in NMOSD patients. There is a pressing need to understand symptom clusters and relationships between multiple symptoms in NMOSD patients.

Network analysis is a popular graphical statistical technique used to analyze complex, multifactorial processes and phenomena and to visualize interactions or relationships between different variables [13,14]. This method compensates for the failings of traditional analyses (e.g., regression) in epidemiology that cannot fully explain the specific pathways in the complex variable set [13]. In recent years, network analysis has been applied in populations with chronic diseases (e.g., cancer, disabilities) [9,15] or psychological disorders (e.g., anxiety, depression) [16,17] to capture complex relationships among symptoms. However, few research applied this methodology to explore the symptom or symptom clusters in NMOSD patients.

Therefore, we conducted a cross-sectional survey to identify symptom clusters in NMOSD patients and explore the core symptoms, symptom clusters, and the relationship between symptoms through network analyses.

2. Methods

2.1. Study design

We conducted an online cross-sectional survey in China between October 10 to 30, 2023. This study was reported by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and registered in the Chinese Clinical Registry Center (No. ChiCTR2300077533).

2.2. Study participants and settings

Participants were recruited online using the convenience sampling method. Inclusion criteria were as follows: 1) diagnosed with NMOSD by neurologists based on European Federation of Neurological Societies (EFNS) guidelines on diagnosis and management of neuromyelitis optica [18]; 2) aged 18 years and over; and 3) informed consent. Participants were excluded if they were: 1) pregnant or breastfeeding women; 2) combined with other serious, chronic comorbidities or acute illnesses, such as malignant tumors, severe liver/renal dysfunctions, or cardiovascular disease; 3) diagnosed with mental illness or dementia and unable to communicate verbally.

Sample size calculation was performed according to Mumtaz et al. [19]. A minimum of 145 participants was required for the network analysis based on five to six individuals per node, with 29 nodes in the current study. Meanwhile, considering invalid questionnaires and expanding the sample size by 10%, the total sample size was 160.

2.3. Measurements

2.3.1. Sociodemographic and clinical data

The sociodemographic variables included age, gender, educational level, employment status, marital status, primary caregiver, insurance type, and personal monthly income. Health-related behavior variables included smoking status and drinking status. Disease-related variables included duration of NMOSD, number of relapses, and polypharmacy.

2.3.2. Self-reported symptoms

A self-made NMOSD symptoms scale was used to evaluate the past week's symptoms in NMOSD patients. The questionnaire was designed based on the framework of the Revised Symptom Management Conceptual Model [20], which is one of the most widely used theoretical frameworks to investigate and manage symptoms. The initial questionnaire was developed through a literature review and group discussions. After two rounds of Delphi expert consultation and pre-survey, the final version of the questionnaire was produced.

The final NMOSD symptoms scale comprises 29 NMOSD-related symptoms, each rated with "yes" or "no" binary responses. If the symptoms were rated with "yes", which indicated that a symptom had occurred in the past week, they would be further measured by their frequency, severity, and distress. The frequency and severity of symptoms were measured using a four-Likert scale (1 = "rarely" to 4 = "always" for frequency, 1 = "mild" to 4 = "very severe" for severity). The distress level of symptoms was measured using a five-Likert scale (0 = "not at all" to 4 = "very much"). The mean value of each dimension was calculated to obtain the symptom burden score. The formula for calculating the prevalence of symptoms is as follows: number of people with symptoms (symptom was rated with "yes")/number of people investigated$\times$100%. In the current study, Cronbach's α coefficient for the NMOSD symptoms scale was 0.976, indicating good internal consistency. The content validity for the scale was 0.96, and the item content validity index ranged from 0.85 to 1.00, indicating good and acceptable content and face validity. The final NMOSD symptoms scale is shown in Appendix A.

2.4. Data collection

The questionnaire was designed and administered using the Wenjuanxing software. The online questionnaire consisted of three parts: 1) the instructions and the precautions for filling in the questionnaire; 2) sociodemographic and clinical data; and 3) self-reported symptoms. All questionnaires were delivered and completed by participants via the WeChat group (https://weixin.qq.com/) of NMOSD, which includes 206 patients who were diagnosed with NMOSD in the Second Affiliated Hospital of Guangzhou University of Chinese Medicine. Participants could access and complete the questionnaires anonymously via a computer, pad, or mobile phone, which can open a hyperlink or scan a Quick Response code. For patients unable to complete the questionnaire,

their family members would fill it out on their behalf. Only one submission was allowed for each IP address, mobile phone, or computer to prevent duplications. Missing responses would be automatically reminded before submission, and only fully completed questionnaires were allowed to be submitted. The questionnaire was sent twice to the WeChat group at three-day intervals. A text message reminder was sent to the mobile phones of non-respondents one week later to increase the response rate. Finally, 151 completed questionnaires were received, of which 140 were valid, with an effective rate of 92.72%.

2.5. Quality control

To ensure the clarity and readability of the questionnaire, we conducted a face-to-face pretest involving five NMODS patients with different education levels before launching the survey. The questionnaires were revised based on the feedback provided. During the formal study, multiple quality control methods were used. Questionnaire completion time was estimated to be about 10 min. A questionnaire was considered invalid if one of the following conditions was met: 1) the time to complete the entire questionnaire was too short (less than 5 min); 2) more than 15 items of questionnaires were filled with the same answer continuously; 3) participants who did not meet the inclusion criteria.

2.6. Data analysis

2.6.1. Descriptive analysis and cluster analysis

All statistical analyses were performed using SPSS (version 26.0) or R (version 4.3.2). We calculated descriptive statistics for all variables reporting means and standard deviations (*SD*) for continuous data and frequencies (n) and percentages (%) for categorical data. Kolmogorov–Smirnov tests were used to test for normality. For continuous data that do not conform to normal distribution, we used means and interquartile range (IQR). Hierarchical cluster analyses [21] were performed with the default cluster hierarchical clustering algorithm. This approach uses a set of dissimilarities for clustering n objects. In the beginning, every measurement period is assigned to its cluster, and the algorithm iteratively merges the two clusters that are most similar at each step. Distances between clusters were recalculated at each step using the Lance–Williams dissimilarity update formula based on the specific clustering method applied. The complete linkage method was applied to find similar clusters. $P < 0.05$ was considered statistically significant.

2.6.2. Network analysis

Network analyses were performed to explore the relationships among symptoms and symptom clusters. All network analyses were conducted using R. R-package “qgraph” (Version 1.9.5) and “bootnet” (Version 1.5.6) were used for network estimation [14]. The cor_auto ( ) function in the qgraph package determined the correlation matrix. The R package qgraph automatically implemented the glasso regularization to transform the correlation analyses into network structures. The Extended Bayesian Information Criterion (EBIC) model was adopted [22]. In network analysis, each symptom is represented as a ‘node,’ and the link between two nodes is shown as an ‘edge.’ A thicker edge indicates a stronger correlation.

Three centrality indices of node centrality were estimated within the network, including strength, closeness, and betweenness [23,24]. Strength centrality refers to the absolute sum of the edge weights connected to a specific node, including all positive and negative edges. Strength centrality (r_s) represents the importance of that node in the network. Closeness centrality (r_c) is determined by the average distance between a node and all other nodes in the network. Betweenness centrality (r_b) is estimated by the number of times a node is located on the shortest path between two different nodes, indicating the network’s degree of connectivity. The “centralityPlot” function in the “qgraph” package was used to calculate centrality indices [25].

A non-parametric bootstrapping method was applied to evaluate the accuracy of edge weights by computing new datasets with 95%*CI* [14]. Case-dropping bootstrap analysis was performed to assess the stability of centrality indices to produce a correlation stability (CS) coefficient, generally less than 0.25 and preferably greater than 0.50 [14].

2.7. Ethical considerations

The Institutional Review Board of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine approved this study (No. BE2023-096-01).

3. Results

3.1. Characteristics of the participants

A total of 140 participants were analyzed in the current study. The median age was 40, ranging from 18 to 73, with a majority being female (87.9%) and married (74.3%). More than half of the participants held a college degree or higher (52.9%) and were none/self-care (58.6%). The median duration of NMOSD was 46.85 months, ranging from 0.5 to 304.6 months, and the median number of relapses was 2 (Table 1).

3.2. Prevalence and burden level of symptoms

The prevalence and the composite score of each symptom perceived by NMOSD patients are shown in Table 2. The most common symptom was pain (n = 92, 65.7%), followed by paraesthesia (n = 91, 65.0%), fatigue (n = 91, 65.0%), easy awakening (n = 89, 63.6%), feeling sleepy (n = 81, 57.9%), difficulty falling asleep (n = 78, 55.7%). Regarding the burden level of symptoms, pain [1.67, (0, 2.58)] was the most burdensome symptom, followed by paraesthesia [1.33, (0, 2.33)], easy awakening [1.33, (0, 2.33)], fatigue [1.00, (0, 2.33)] and difficulty falling asleep [1.00, (0, 2.00)]. The symptom scores of each dimension (frequency, severity, and distress) are shown in Appendix A.

3.3. Symptom clusters analysis

Six clusters were identified from the hierarchical cluster analysis, as shown in Fig. 1. The symptoms in each of the six clusters are described as follows: cluster#1: somatosensory symptom (four items): pain, somatosensory disorders, paraesthesia, and constipation; cluster#2: motor symptoms (four items): motor dysfunction, ataxia, muscle weakness, and limb spasticity; cluster#3: visual and memory symptom (four items): visual impairment, diplopia, memory decline, and dizziness, cluster#4: bladder and rectum symptoms (six items): dysuria, frequent urination, urgent urination, nocturia, urinary retention, and decreased bowel control, cluster#5: sleep symptoms (three items): difficulty falling asleep, easy awakening, and insomnia, cluster#6: neuropsychological symptom (eight items): feeling sleepy, fatigue, lack of concentration, feeling nervous, feeling anxious, feeling depressed, feeling irritable, and feeling sad.

Table 1
Characteristics of the participants ($n = 140$).

Characteristics	Categories	*n* (%)
Age (years)	18–25	13 (9.3)
	26–35	30 (21.4)
	36–45	47 (33.6)
	≥46	50 (35.7)
Sex	Male	17 (12.1)
	Female	123 (87.9)
Educational level	Primary school or below	7 (5.0)
	Secondary school	30 (21.4)
	High school	29 (20.7)
	University or above	74 (52.9)
Employment	Mental workers	67 (47.8)
	Manual workers	48 (34.3)
	None	25 (17.9)
Marital status	Married	104 (74.3)
	Unmarried	30 (21.4)
	Divorced	4 (2.9)
	Widow	2 (1.4)
Primary caregivers	Relatives	55 (39.3)
	Friends/nanny	3 (2.1)
	None/self-care	82 (58.6)
Insurance type	Socialized medicine	5 (3.6)
	UEBMI	86 (61.4)
	URBMI	12 (8.6)
	NRCMS	26 (18.6)
	Self-pay	11 (7.8)
Personal monthly income (yuan)	None	48 (34.3)
	<3,000	30 (21.4)
	3,000–6,000	39 (27.9)
	>6,000	23 (16.4)
Smoking	Never smoker	131 (93.6)
	Former smoker	4 (2.8)
	Current smoker	5 (3.6)
Drinking	Never drinker	130 (92.9)
	Former drinker	8 (5.7)
	Current drinker	2 (1.4)
Duration of disease (months)	≤12	33 (23.6)
	13–36	23 (16.4)
	37–60	27 (19.3)
	≥61	57 (40.7)
Number of relapses	≤2	84 (60.0)
	3–4	20 (14.3)
	≥5	36 (25.7)
Polypharmacy (≥5)	No	74 (52.9)
	Yes	66 (47.1)

Note: UEBMI = urban employee-based basic medical insurance. URBMI = urban resident-based basic medical insurance. NRCMS = new rural cooperative medical scheme.

3.4. Symptom networks and centrality indices

3.4.1. Analysis of symptom networks

Fig. 2 shows the overall networks of symptoms. The three strongest edges were between "frequent urination" and "urgent urination" ($r = 0.43$), "difficulty falling asleep" and "insomnia" ($r = 0.39$), "pain" and "paraesthesia" ($r = 0.38$). Fig. 3 presents three centrality indices: strength, betweenness, and closeness. Fatigue was the most central symptom across the three centrality indices of strength ($r_s = 12.388$), betweenness ($r_b = 68$), and closeness ($r_c = 0.015$), followed by ataxia ($r_s = 12.207$, $r_b = 24$, $r_c = 0.015$) and memory decline ($r_s = 11.670$, $r_b = 22$, $r_c = 0.014$). Fatigue was the most prominent bridge symptom ($r_b = 68$), followed by ataxia ($r_b = 24$) and memory decline ($r_b = 22$). The detailed information for centrality indices is shown in Appendix A.

Edge accuracy analyses show that the 95%*CIs* of most estimated edge weights of the symptom network were narrow, suggesting that the estimates were accurate and reliable. Regarding the stability of the estimated centrality indices, the correlation stability coefficient of the overall symptom network was 0.257 for both strength and closeness, suggesting that the overall symptom network was stable (Appendix A).

Table 2
The prevalence and burden level of symptoms among the participants.

Symptoms	Prevalence	Burden level
	n (%)	*Median* (P_{25}, P_{75})
D1: Pain	92 (65.7)	1.67 (0, 2.58)
D2: Somatosensory disorders	75 (53.6)	1.00 (0, 2.33)
D3: Paraesthesia	91 (65.0)	1.33 (0, 2.33)
D4: Constipation	61 (43.6)	0 (0, 1.92)
D5: Motor dysfunction	57 (40.7)	0 (0, 1.67)
D6: Ataxia	48 (34.3)	0 (0, 1.25)
D7: Muscle weakness	57 (40.7)	0 (0, 1.67)
D8: Limb spasticity	50 (35.7)	0 (0, 1.33)
D9: Visual impairment	52 (37.1)	0 (0, 1.33)
D10: Diplopia	55 (39.3)	0 (0, 1.33)
D11: Memory decline	75 (53.6)	0.83 (0, 1.67)
D12: Dizziness	59 (42.1)	0 (0, 1.33)
D13: Dysuria	38 (27.1)	0 (0, 1.00)
D14: Frequent urination	49 (35.0)	0 (0, 1.25)
D15: Urgent urination	41 (29.3)	0 (0, 1.00)
D16: Nocturia	57 (40.7)	0 (0, 1.33)
D17: Urinary retention	23 (16.4)	0 (0, 0)
D18: Decreased bowel control	25 (17.9)	0 (0, 0)
D19: Difficulty falling asleep	78 (55.7)	1.00 (0, 2.00)
D20: Easy awakening	89 (63.6)	1.33 (0, 2.33)
D21: Insomnia	75 (53.6)	1.00 (0, 1.33)
D22: Feeling sleepy	81 (57.9)	1.00 (0, 1.67)
D23: Fatigue	91 (65.0)	1.33 (0, 2.33)
D24: Lack of concentration	50 (35.7)	0 (0, 1.33)
D25: Feeling nervous	52 (37.1)	0 (0, 1.33)
D26: Feeling anxious	71 (50.7)	0.67 (0, 1.67)
D27: Feeling depressed	47 (33.6)	0 (0, 1.00)
D28: Feeling irritable	55 (39.3)	0 (0, 1.33)
D29: Feeling sad	56 (40.0)	0 (0, 1.33)

3.4.2. Analysis of symptom clusters

Fig. 4 shows the network of symptom clusters and centrality indices. The three strongest edges were between "motor symptom" and "somatosensory symptom" ($r = 0.43$), "neuropsychological symptom" and "visual and memory symptom" ($r = 0.40$), "neuropsychological symptom" and "sleep symptom" ($r = 0.31$). "Motor symptom" ($r_s = 2.68$, $r_c = 0.10$) was the most central symptom cluster among the six clusters, followed by "neuropsychological symptom" ($r_s = 2.65$, $r_c = 0.10$), and "visual and memory symptom" ($r_s = 2.39$, $r_c = 0.09$). The most central symptoms of each symptom cluster were pain, ataxia, memory decline, urgent urination, easy awakening, and fatigue.

Edge accuracy analyses show that the 95%*CIs* of most estimated edge weights were generally not wide, suggesting that the estimates were accurate and reliable. The strength, closeness, and betweenness were 0.514, 0.364, and 0.364, respectively, suggesting that the networks of symptom clusters were stable (Appendix A).

4. Discussion

This study is the first to identify the symptom clusters and core symptoms and explore their interrelationships among symptoms in NMOSD patients. The main findings are: 1) pain was the most prevalent and burdensome symptom in NMOSD patients; 2) fatigue was the most central and prominent bridge symptom in the whole symptom network; 3) six clusters were identified in NMOSD patients, including somatosensory symptom cluster, motor symptom cluster, visual and memory symptoms cluster, bladder and rectum symptom cluster, sleep symptoms cluster, and neuropsychological symptom cluster; "motor symptom" was the most central symptom cluster among the six clusters. These results were robust to

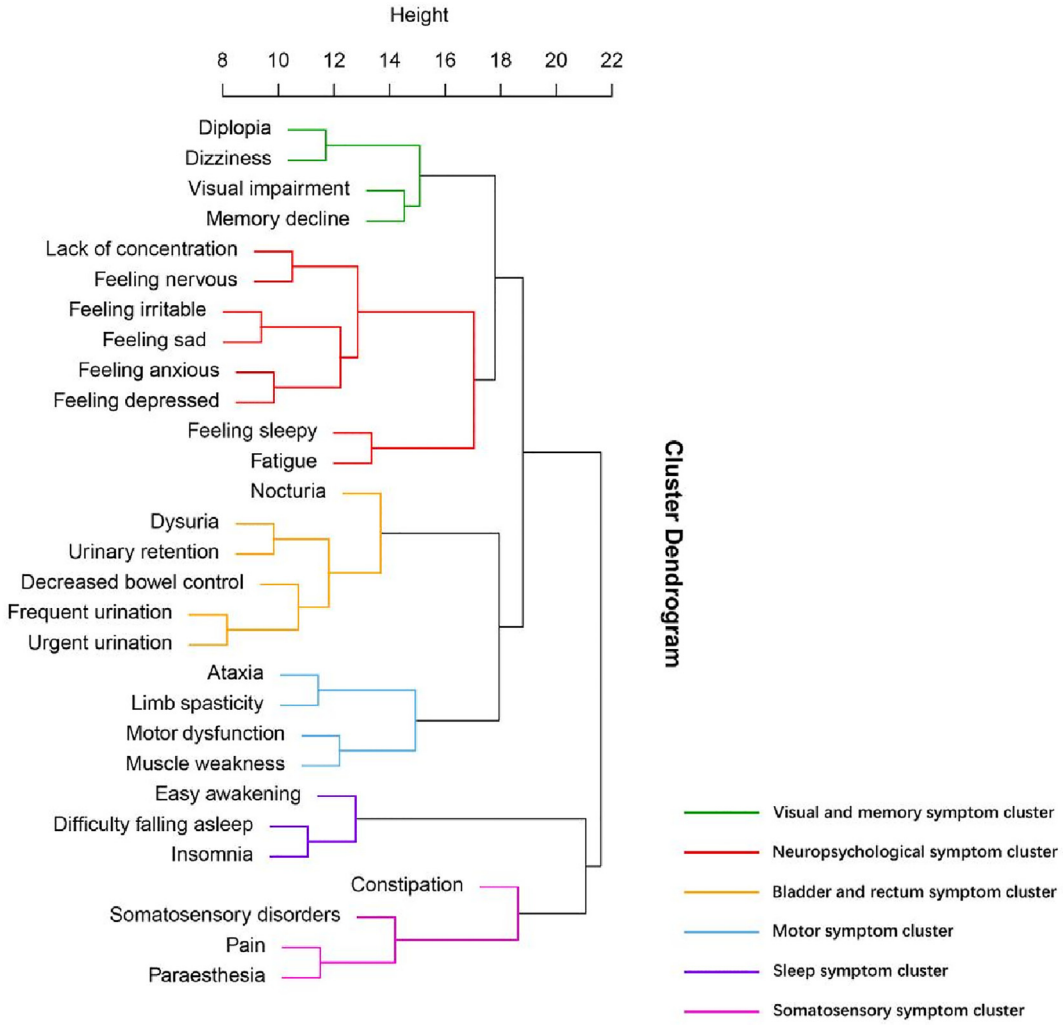

Fig. 1. Cluster analysis of symptoms in patients with neuromyelitis optica spectrum disorder.

accuracy and stability tests and provide a novel perspective for understanding multiple symptoms in NMOSD patients.

Pain is a common symptom of NMOSD patients. In our study, we found that pain was the most prevalent and burdensome symptom in NMOSD patients, with the highest scores across the frequency, severity, and distress domains, which were consistent with previous research results [7,26]. These results indicated that assessment and treatments targeting pain in NMOSD are essential. It was reported that common NMOSD pain includes neuropathic pain, eye pain, painful tonic spasms, and headache [26,27]. Our previous study found that the prevalence of neuropathic pain in NMOSD patients was 43.0% [28]. However, the incidences among different types of pain were not assessed in this study. Relapse-related treatments and immunomodulatory treatment are currently the most common modality of pain treatment in NMOSD [27]. However, the current management of pain in NMOSD is not sufficient, and there are relatively few published studies regarding the intervention or treatment of pain in NMOSD. Therefore, We call for healthcare personnel and future studies to pay more attention to a multidisciplinary approach to pain management based on the respective pain type.

Another important finding of the current study was identifying central and bridge symptoms in the symptom network of NMOSD. In a theoretical network model, central symptoms play a significant role in causing the onset of a syndrome and contribute the majority to the network maintenance [29]. Bridge symptoms were considered an illness pathway for one disorder to spread to another, and interventions targeting bridge symptoms may disrupt maintenance loops [24]. In the current study, we found that fatigue emerged as both the strongest central symptom and bridge symptom in the NMOSD symptom network. This suggests that fatigue was vital in triggering and maintaining the symptom network among NMOSD patients. There has been a great deal of research exploring fatigue in multiple sclerosis, including symptom burden [30], management [31], and pathophysiological mechanisms [32]. The concept of “multiple sclerosis-related fatigue” was also proposed [33]. However, less attention has been paid to exploring fatigue in NMOSD patients. It was recognized that fatigue was a significant predictor for QOL in patients with NMOSD [34,35]. A comparative study found that fatigue was the only independent predictor that predicted both mental and physical components of QOL in patients with NMOSD [35]. Moreover, It has been reported that fatigue was not only associated with severe depression and severe pain intensity but also with hypoxemia and poor sleep quality in NMOSD patients [34,36]. Taken together, it is crucial to address fatigue not only because this would maintain high quality of life but also because it coexists with the other symptoms and contributes to one another.

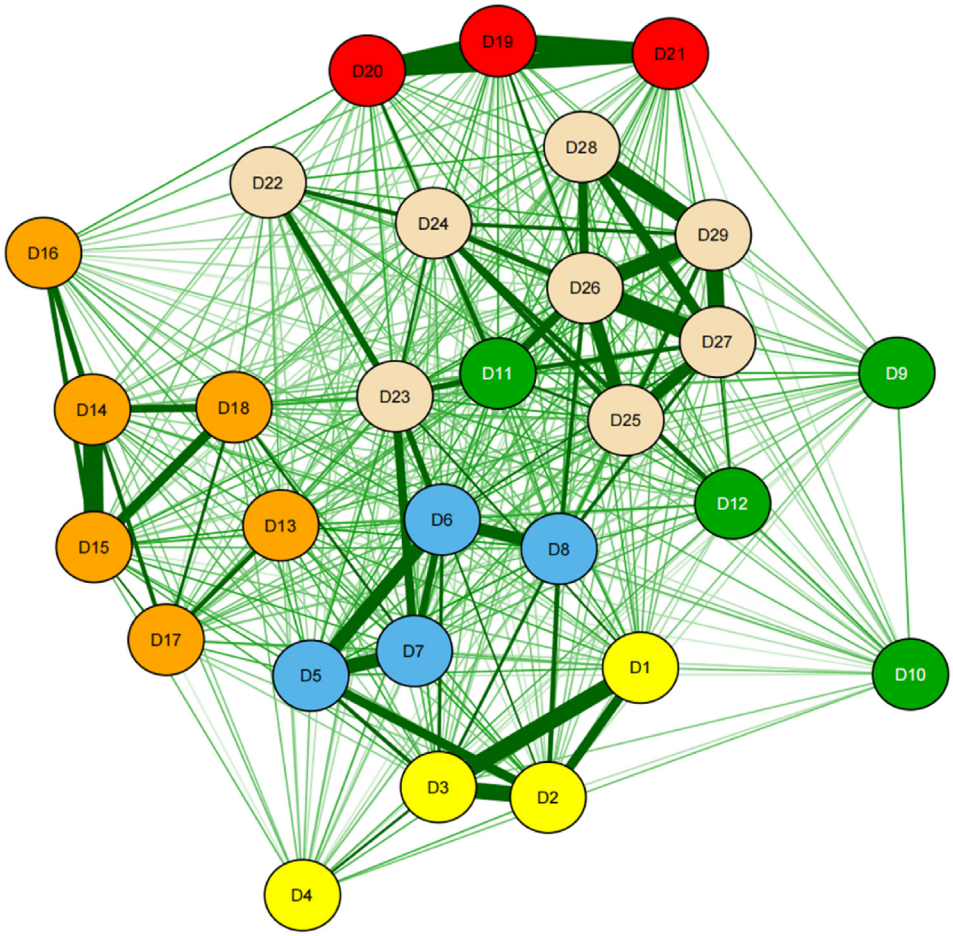

Fig. 2. Network of symptoms for patients with neuromyelitis optica spectrum disorder.
D1: Pain. D2: Somatosensory disorders. D3: Paraesthesia. D4: Constipation. D5: Motor dysfunction. D6: Ataxia. D7: Muscle weakness. D8: Limb spasticity. D9: Visual impairment. D10: Diplopia. D11: Memory decline. D12: Dizziness. D13: Dysuria. D14: Frequent urination. D15: Urgent urination. D16: Nocturia. D17: Urinary retention. D18: Decreased bowel control. D19: Difficulty falling asleep. D20: Easy awakening. D21: Insomnia. D22: Feeling sleepy. D23: Fatigue. D24: Lack of concentration. D25: Feeling nervous. D26: Feeling anxious. D27: Feeling depressed. D28: Feeling irritable. D29: Feeling sad.

This suggests that medical staff and caregivers should pay more attention to fatigue when formulating health care plans for NMODS patients. Additional research is required in the future to focus on NMODS-related fatigue, including the potential mechanism and optimal management strategies.

Six symptom clusters were identified from our data. The compositions of these symptom clusters were expected, except for the somatosensory symptom cluster. It is not surprising that the symptoms of pain, somatosensory disorders, and paraesthesia were included in the somatosensory symptom cluster. Interestingly, constipation symptoms were also included. We speculated the reason for this result is related to the association between neuropathic pain and constipation in NOMDS. A survey study from the United States found that neuropathic pain and constipation coexisted in 43.5% of the surveyed participants with NMOSD or myelin oligodendrocyte glycoprotein antibody disease. The majority of patients with both symptoms reported that the severity of neuropathic pain was increased with worse constipation [37]. However, the pathophysiological mechanisms underlying this relationship remain unclear. Additionally, we found that the motor symptom cluster was the most central in the network, strongly associated with somatosensory symptoms, visual and memory symptoms, neuropsychological symptoms, and bladder and rectum symptoms. These findings indicate a tight linkage among NMOSD symptom clusters, and the motor symptom cluster has the greatest impact on network maintenance. According to network theory, interventions targeting core symptoms should have maximal effects in decreasing all symptoms within the network. Therefore, intervention strategies targeting motor symptom clusters are essential to remiss the overall symptom burden in patients with NMOSD.

Several limitations should be noted in this study. First, this study is an online survey, and the participants voluntarily enrolled, which may lead to selection bias. Patients who can fill out online questionnaires are more likely to be in the younger group and experience milder symptoms. As a result, the sample may not be a good representation of the overall NMODS patients. The extrapolation of this studys results should be done with caution. Second, there is no symptom scale for the NMODS patients in the current literature, so this study uses a self-edited questionnaire. Despite showing good reliability and validity in the current study, the NMOSD symptoms scale needs more research to prove its validity. Third, although the final valid sample of 140 approached the target sample size of 145, we cannot overlook the small sample size in creating statistical uncertainties which may further affect the reliability of the conclusion. Future studies with larger samples are needed to corroborate our findings.

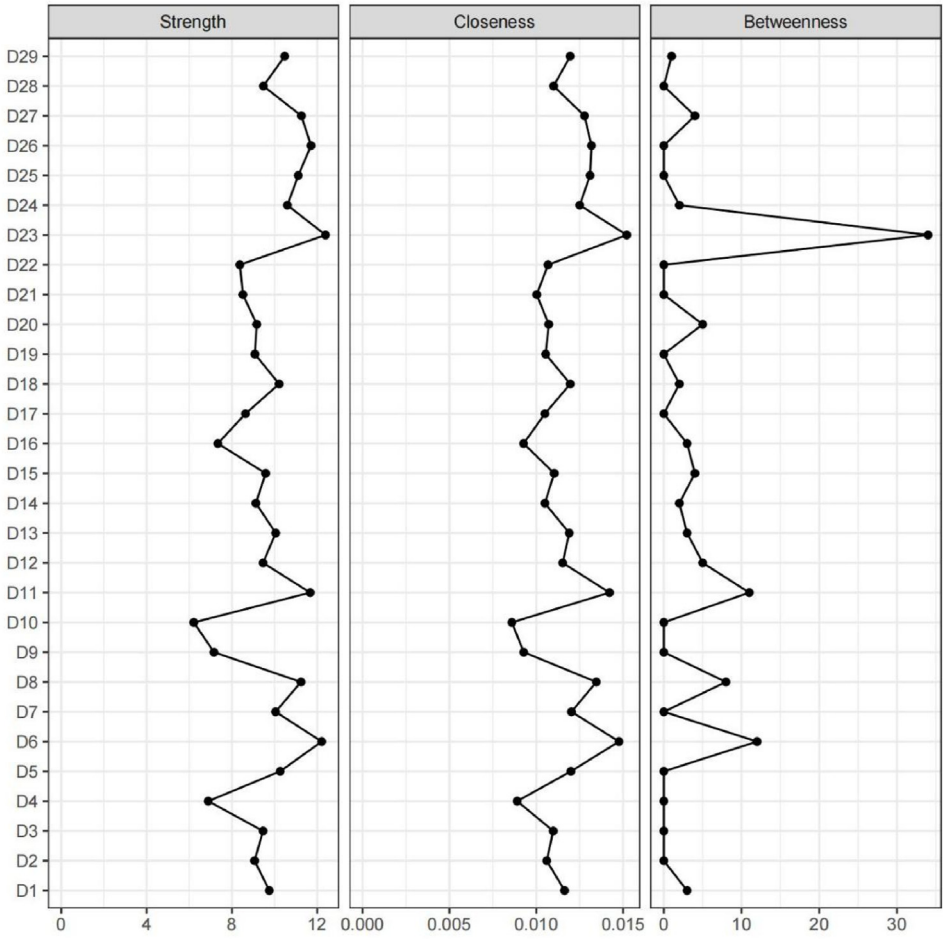

Fig. 3. Strength, closeness, and betweenness centrality measures for the network of symptoms in patients with neuromyelitis optica spectrum disorder.
D1: Pain. D2: Somatosensory disorders. D3: Paraesthesia. D4: Constipation. D5: Motor dysfunction. D6: Ataxia. D7: Muscle weakness. D8: Limb spasticity. D9: Visual impairment. D10: Diplopia. D11: Memory decline. D12: Dizziness. D13: Dysuria. D14: Frequent urination. D15: Urgent urination. D16: Nocturia. D17: Urinary retention. D18: Decreased bowel control. D19: Difficulty falling asleep. D20: Easy awakening. D21: Insomnia. D22: Feeling sleepy. D23: Fatigue. D24: Lack of concentration. D25: Feeling nervous. D26: Feeling anxious. D27: Feeling depressed. D28: Feeling irritable. D29: Feeling sad.

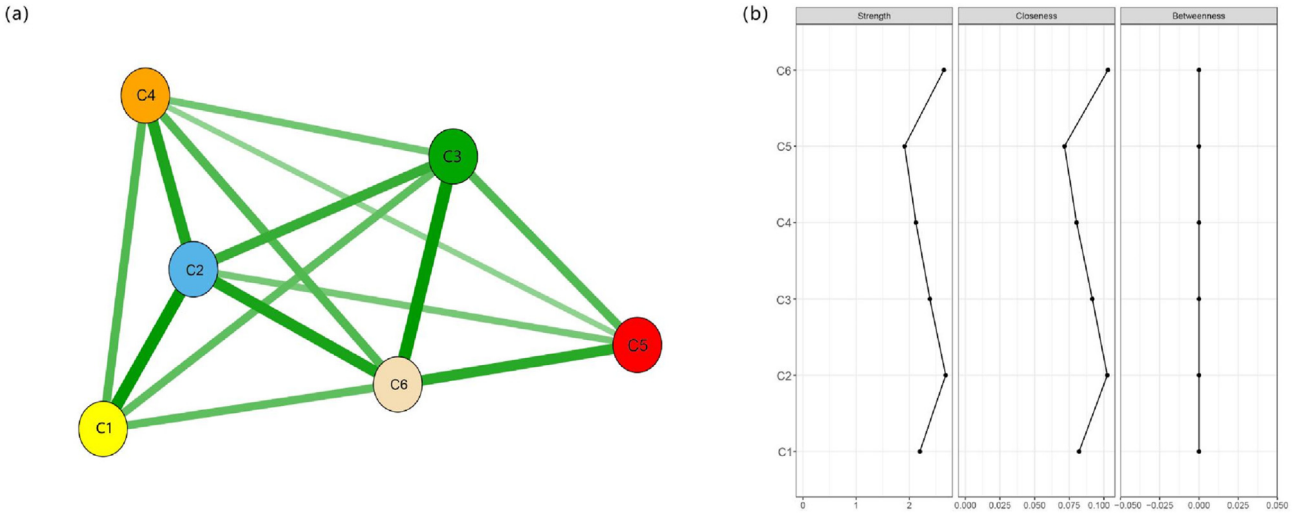

Fig. 4. Network of symptom clusters and centrality indices in patients with neuromyelitis optica spectrum disorder. (a): Network of symptom clusters. (b): Strength, closeness, and betweenness centrality measures for the network of symptom clusters.
C1: Somatosensory symptom cluster. C2: Motor symptom cluster. C3: Visual and memory symptom cluster. C4: Bladder and rectum symptom cluster. C5: Sleep symptom cluster. C6: Neuropsychological symptom cluster.

5. Conclusions

Pain was the most prevalent and burdensome symptom in NMOSD patients. Fatigue was the most central and prominent bridge symptom in the symptom network. Six clusters were identified in NMOSD patients, including somatosensory symptom cluster, motor symptom cluster, visual and memory symptoms cluster, bladder and rectum symptom cluster, sleep symptoms cluster, and neuropsychological symptom cluster. Motor symptom was the most central symptom cluster among the six clusters. Identifying the core and bridge symptoms and core symptom clusters in NMOSD patients will enable nurses to develop targeted symptom management strategies focusing on key symptoms and symptom clusters. Future studies are warranted to establish dynamic symptom networks based on real-world clinical follow-up data to explore the longitudinal changes in symptom clusters, core symptoms, and network density.

CRediT authorship contribution statement

Hao Liang: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Jiehan Chen:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing, Supervision, Project administration. **Lixin Wang:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision, Project administration. **Zhuyun Liu:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing. **Haoyou Xu:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision. **Min Zhao:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. **Xiaopei Zhang:** Conceptualization, Methodology, Validation, Formal analysis, Funding acquisition, Writing – review & editing, Supervision, Project administration.

Data availability statement

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no competing interests.

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Appendices. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijnss.2025.02.006.

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