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RESEARCH ARTICLE

Mortality of neuromyelitis optica spectrum disorders in a Chinese population

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Abstract

Objective: Neuromyelitis optica spectrum disorder (NMOSD) is a rapidly disabling disease. Epidemiologic studies have suggested varying NMOSD mortality across ethnic groups. However, NMOSD mortality data in China are scarce. This study's objectives were to explore mortality and causes of death among Chinese NMOSD patients and to identify independent predictors of death. **Methods**: We performed a retrospective study with a 10-year follow-up of Chinese NMOSD patients. A Cox proportional hazards model was used to identify independent predictors of death. **Results**: Five hundred and sixty-nine patients were included; 24 patients died during follow-up, for overall mortality of 4.2%. In these patients, the median disease duration at the time of death was 3.4 years. The most common cause of death was secondary infection (62.5%), especially respiratory infection (45.8%). The second most common cause of death was extensive cervical myelitis with respiratory failure (16.7%). Other causes included suicide (8.3%), cancer (4.2%), cerebral embolism (4.2%), and unknown causes (4.2%). The multivariate Cox analyses indicated that a short first interattack interval (HR = 0.93, 95% CI 0.89–0.98, $p = 0.003$), lack of regular immunotherapy (HR = 10.34, 95% CI 4.05–26.37, $p < 0.001$), and older age at onset were independent predictors of death. Every increasing decade of onset age increased the risk of death 2.59 times (95% CI 1.74–3.86, $p < 0.001$). **Interpretation**: Infections were more common in patients not treated with any immunotherapy, indicating that early and consequent immunotherapy might prevent death by infections, which is of great importance for further treatment of NMOSD patients to avoid undertreatment due to fear of treatment-associated infections.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) that mainly presents as optic neuritis (ON), transverse myelitis (TM), and/or area postrema syndrome (APS), with risks of relapse, severe disability, and rarely death.[1,2] A relapsing-remitting clinical course occurs in more than 80% of NMOSD cases.[1] More than 70% of patients have detectable serum anti-aquaporin-4 antibodies (AQP4-Ab), which are considered pathogenic and can be associated with disease relapse.[1,3] NMOSD is a rare disorder with an incidence ranging from 0.72 to 10.0 per 100,000 people,[4–6] and the typical age at onset is between 35 and 42 years old[7,8]; it is particularly common in Asian and South African populations.[6,9]

NMOSD is associated with a poor prognosis, and the severity and degree of recovery from relapses determine long-term visual and motor disabilities as well as mortality.[10] Mortality in NMOSD worldwide ranges from 3.3% to 32% and is determined by age, relapse rate, and recovery from attacks.[10,11] However, data on the mortality of NMOSD in China are scarce.

Therefore, the aim of the present study was to examine the mortality and causes of death in Chinese patients with NMOSD and to detect risk factors associated with death in NMOSD. For this purpose, we performed a mortality

survey among NMOSD patients in the largest medical center in Southwest China.

Methods

Participants

All of the participants were recruited from West China Hospital, Sichuan University, which is currently one of the largest medical centers in China, with the patient population covering more than one-fifth of the Chinese population. From September 2009 to September 2019, we enrolled patients who fulfilled the Wingerchuk 2006 criteria for neuromyelitis optica (NMO)[2] or the revised Wingerchuk 2015 criteria for NMOSD.[1] Patients recruited between 2009 and 2016 fulfilled the Wingerchuk 2006 criteria, and patients recruited after 2016 fulfilled the revised Wingerchuk 2015 criteria. Patients with myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) were excluded. The clinical data of all of the patients were also collected, and all of the participants were followed every 6 months with either in-person or telephone (for patients strictly restricted to a wheelchair or bed) interviews. Magnetic resonance imaging (MRI) studies included axial and sagittal images of the spinal cord obtained by T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and T1-weighted postcontrast sequences. This study was approved by the Medical Ethics Committee of the West China Hospital of Sichuan University (approval number: 2018-29), and informed consent was provided by each participant before enrollment.

Clinical information collection

We collected the following information and entered it into our NMOSD database: demographics, age at onset, disease duration, phenotype at onset, number of relapses, time to the second attack, number of severe attacks, annualized relapse rate (ARR, the number of attacks per patient-year), AQP4-Ab, and MOG-Ab serostatus (cell-based assay, CBA) (EUROIMMUN AG, Lubeck, Germany),[12,13] lesions on spinal MRI, therapeutic regimens (agents, maintenance time, and dosages), and coexisting autoimmune disorders (including systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroid disease, rheumatoid arthritis, connective tissue disease, and so on).

For patients who died during the follow-up period, we reviewed all recent hospital records and the death certificate and visited the patients' relatives or caregivers to identify the age at onset, cause of death, therapeutic regimen, and disease duration.

The daily dosage of mycophenolate mofetil (MMF) for each patient was 20 mg/kg of body weight, and azathioprine (AZA) was started at 25 or 50 mg daily and was increased 2 weeks later to 2 mg/kg of body weight. It seems that most of our NMOSD patients preferred to take MMF over AZA due to concerns about the adverse effects of AZA.[14] Other immunosuppressants included rituximab, tacrolimus, methotrexate, and cyclosporin.

A relapse was defined as a new worsening neurological function with an Expanded Disability Status Scale (EDSS) score increase of at least 0.5 points for more than 24 h in the absence of other identifiable causes, with occurrence more than 30 days after a previous attack or new MRI-detected lesion. A severe attack was defined as acute myelitis with an EDSS score of $\geq$6.0 (unilateral/bilateral assistance needed to walk, wheelchair dependency, restriction to a bed, or even death) or an increase of $\geq$0.5 points if the patient had a baseline EDSS score $\geq$6.0.[15,16] In cases of ON, a severe attack was defined as visual acuity of unilateral or bilateral blindness or light perception (LP). Disability was defined as irreversible motor disability (EDSS score of $\geq$6.0) or irreversible visual impairment (LP or blindness) during remission.

Statistical analysis

Quantitative data were described as numbers (n), frequencies (%), medians (ranges) or means $\pm$ standard deviations (SDs). Kaplan–Meier analysis was used to establish the survival curve of our NMOSD patients. Cox proportional hazards models were constructed to estimate the hazard ratios (HRs) for death and to identify independent risk factors for mortality in NMOSD patients. Covariates, including sex, age at onset (stratified by decade), core symptoms at onset, history of severe onset, history of a severe attack during the disease course, time to the first relapse, ARR, and history of visual or motor disability before death, were evaluated by univariate Cox analyses, and those with a cutoff of $p < 0.1$ were further included in the multivariate Cox analysis to determine independent risk factors for mortality in NMOSD patients. HRs and 95% confidence intervals (CIs) were calculated to estimate the risks associated with predictors. All of the statistical analyses were conducted using SPSS software, version 25.0 (IBM Corp., Armonk, NY, USA). The level of significance was defined by a 2-tailed p-value of <0.05 in the multivariate Cox regression analysis.

Results

Demographic and disease-related characteristics

In all, 642 patients with NMOSD were investigated in this study and 73 patients were excluded due to loss to

Table 1. Demographic, clinical, therapeutic, and prognostic characteristics of all the enrolled patients with NMOSD.

Variables	NMOSD
Sex, female, *n* (%)	505 (88.8)
AQP4-Ab, positive, *n* (%)[1]	516 (90.7)
Age, median (range), years	47.3 (15.3–83.8)
Disease duration, median (range), years	5.3 (0.1–39.6)
Age at onset, median (range), years	39.6 (12.3–78.4)
Autoimmune comorbidity, *n* (%)	163 (28.6)
Time to the second attack, median (range), months[2]	10.0 (1.0–292.2)
ARR, median (range)[3]	0.67 (0.10–3.85)
Visual disability (blindness or light perception), *n* (%)	106 (18.6)
Motor disability (EDSS scores ≥6.0), *n* (%)[4]	96 (17.0)
Treatment for the prevention of relapse	
Regular immunosuppressant use for >1 year, *n* (%)	451 (79.2)
MMF	314 (55.2)
AZA	89 (15.6)
RTX	13 (2.3)
Other immunosuppressant use	35 (6.2)
Irregular immunosuppressant use for <1 year, *n* (%)	50 (8.8)
Nonimmunotherapy, *n* (%)	68 (12.0)

AQP4-Ab, aquaporin-4 antibody; ARR, annualized relapse rate; AZA, azathioprine; EDSS, Expanded Disability Status Scale; MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorder; RTX, rituximab; *n*, number.

[1]A patient with unknown AQP4-Ab status.

[2]71 patients were excluded from the analysis because of monophasic disease durations.

[3]21 patients were excluded from the analysis because of disease durations ≤12 months.

[4]Three patients were excluded from the analysis due to death within 6 months of a severe motor attack.

follow-up. Ultimately, 569 patients were enrolled in the analysis. The demographic and clinical characteristics of the patients with NMOSD are presented in Table 1.

During the 10-year follow-up, a total of 24 patients (female:male = 19:5) died, and 22 were seropositive for AQP4-Ab. The median age at onset of the deceased subjects was much older than that of the NMOSD patients in our database (53.3 vs. 39.6 years old; $p < 0.001$). The median disease duration at the time of death of the deceased patients was 3.4 years (Fig. 1). The demographic and clinical characteristics of these patients are shown in Table 2.

Of the 24 deceased patients, disease onset presented as a TM attack more frequently (58.3%) than an ON attack (37.5%), and TM (95.8%) was more frequently observed than ON (62.5%) in the disease duration. The co-occurrence of ON and TM was present in 58.3% of subjects and APS occurred in only 16.7%. In addition, 58.3% of the patients presented with severe attacks at onset, of which 33.3% were motor and 25.0% were visual attacks. Severe attacks were observed in up to 95.8% of individuals during the disease course, and 37.5% and 83.3% of cases presented with severe visual and motor episodes, respectively; 25.0% suffered from both visual and motor forms. A relapsing form was observed in 95.7% of cases. The median ARR was 1.2 (range 0.4–3.9), with a median first interattack interval of 3.7 months (range 1.0–43.5 months). The last median EDSS score before death was 8.8 (range 3.0–9.5). We found that 90.0% of the patients experienced longitudinally extensive transverse myelitis during the disease course. The most common location was the cervical area, followed by the thoracic area. Coexisting autoimmune diseases were observed in 29.2% of the cases. A total of 37.5% of patients took immunosuppressants for relapse prevention. A total of 71.4% of patients experienced sustained disability during the disease course, and motor disability (61.9%) was more common than visual disability (29.2%).

In addition, most of the deceased patients had an education level less than junior middle school, and approximately one-third were illiterate. Most were farmers with low incomes and had a low frequency of active follow-up.

Causes of death in patients with NMOSD

As shown in Table 3, the most common cause of death in patients with NMOSD was secondary infection (15, 62.5%), including respiratory infection (11, 45.8%), viral infection (2, 8.3%), and sepsis (2, 8.3%). Of the 15 patients who died from secondary infections, 5 received immunosuppressants for relapse prevention and 10 did not take any immunosuppressants, including corticosteroids. The proportion of patients taking immunosuppressants was much smaller than that of the other patients in our database. The second most common cause of death was extensive cervical myelitis with respiratory failure (4, 16.7%). Two patients (8.3%) died of suicide, one patient (4.2%) died of cervical cancer, one patient (4.2%) died of cerebral embolism, and one patient (4.2%) died of an unknown cause.

Analyses of predictors for death in patients with NMOSD

For the deceased subjects, Cox regression analyses were used to explore potential predictors. Two patients who committed suicide were excluded from the analysis. Univariate Cox regression analysis indicated that male sex, age at onset, history of a severe motor attack, time to the

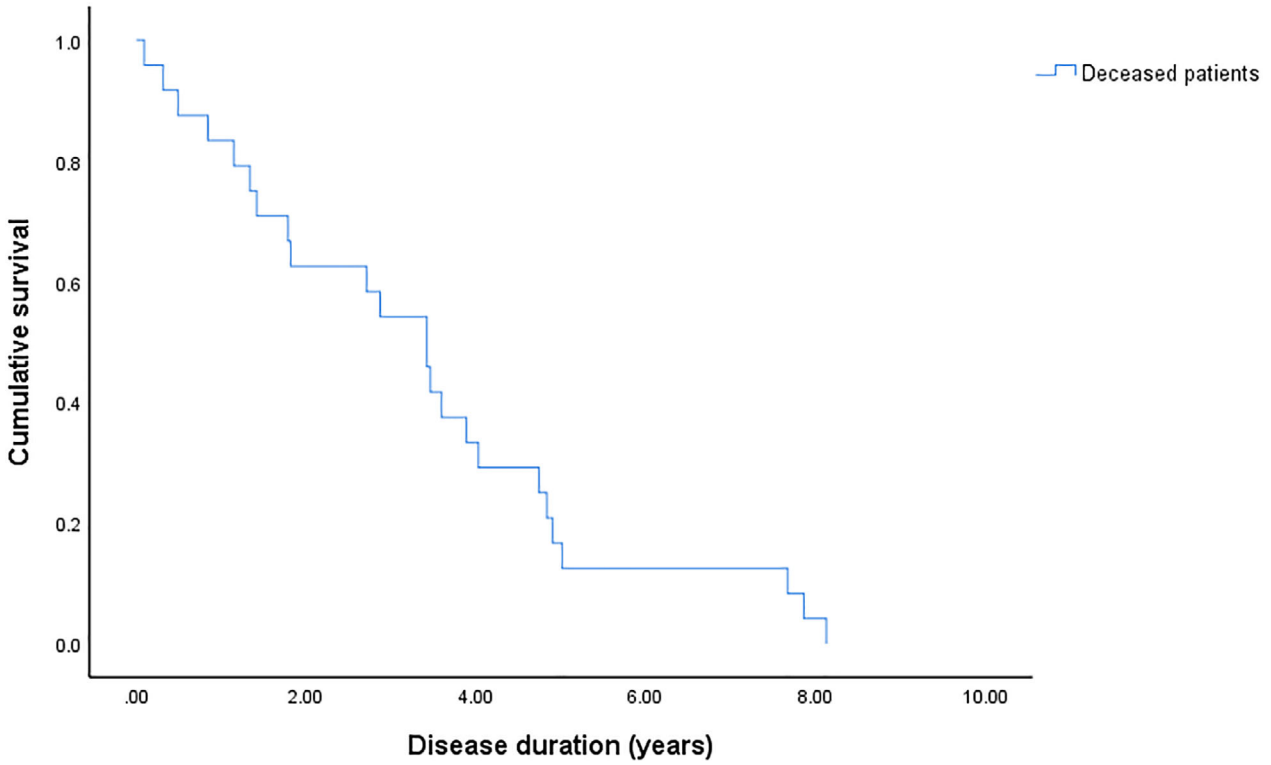

Figure 1. Kaplan–Meier survival curve of the 24 deceased NMOSD patients. The median survival from symptom onset to death was 3.4 years.

second attack, ARR, history of motor disability before death, and lack of regular immunotherapy were associated with the risk of death. Subsequently, the multivariate Cox regression analysis confirmed that patients with a short first interattack interval (HR = 0.93, 95% CI 0.89–0.98, $p = 0.003$), lack of regular immunotherapy (HR = 10.34, 95% CI 4.05–26.37, $p < 0.001$), and older age at onset were independent predictors of death; the Kaplan–Meier analysis results are illustrated in Figure 2. Every increasing decade of age at onset increased the risk of death by 2.59 times (95% CI 1.74–3.86, $p < 0.001$) (Table 4).

Discussion

During the 10-year follow-up in our center, a total of 24 patients with NMOSD died. We found a large proportion of deaths related to NMOSD. Our present study showed that the leading cause of death among NMOSD patients was respiratory infection, followed by extensive cervical myelitis with respiratory failure. Suicide was also a cause of death that should not be ignored. In the past, it was generally believed that the long-term use of immunosuppressants could increase the risk of secondary infections in NMOSD patients, but our observations revealed that, among patients who died from secondary infections, the proportion of those who did not use immunosuppressants (10/15) was much larger than that of those who did in our database (5/15). For the deceased patients who did not use immunosuppressants, half of them suffered from severe TM in their first attacks, and 80% of them developed irreversible motor disability over their disease duration. Coupled with the risk of death from respiratory failure due to severe myelitis, the progression of the disease itself and the risk of secondary infection caused by relapse might be much more relevant than the risk caused by immunosuppressant use alone. A significant proportion of our deceased patients did not receive regular immunotherapy, which could be attributed to poverty and poor education. In addition, our patients mainly came from Southwest China, where the economy is underdeveloped. Conversely, due to the special conditions in China, many patients prefer traditional Chinese medicines and are concerned about the side effects of immunosuppressants, approximately 20% of the patients with NMOSD in our database do not use any immunotherapy, including corticosteroids.

Kitley et al. found that bronchopneumonia (3/10, 33.3%) was the most common cause of death during follow-up since it was the cause in 10 of the 106 enrolled NMOSD patients.[17] In the late stage of the disease, almost

Table 2. Demographic, clinical, therapeutic, prognostic, and MRI characteristics of the deceased patients with NMOSD.

Variables	Subjects
Sex, female, *n* (%)	19 (79.2)
Age at onset, median (range), years	53.3 (26.1–78.4)
Age at death, median (range), years	56.1 (33.8–80.9)
Disease duration, median (range), years	3.4 (0.1–8.1)
AQP4-Ab, positive, *n* (%)[1]	22 (95.7)
Phenotypes at onset, *n* (%)	
ON	9 (37.5)
TM	14 (58.3)
APS	4 (16.7)
Severe attack at onset	14 (58.3)
Severe ON at onset	6 (25.0)
Severe TM at onset	8 (33.3)
Severe attack during the disease course	23 (95.8)
ON	9 (37.5)
TM	20 (83.3)
ON+ TM	6 (25.0)
Phenotypes occur in the disease course	
ON	15 (62.5)
TM	23 (95.8)
ON+ TM	14 (58.3)
APS	4 (16.7)
Relapsing disease course, *n* (%)	22 (95.7)
Time to the second attack, median (range), months[2]	3.7 (1.0–43.5)
ARR, median (range)[3]	1.2 (0.4–3.9)
Autoimmune comorbidity, *n* (%)	7 (29.2)
Patients with disability before death, *n* (%)[4]	15 (71.4)
Visual disability (blindness or light perception), *n* (%)	7 (29.2)
Motor disability (EDSS scores ≥6.0), *n* (%)[4]	13 (61.9)
Visual and motor disability, *n* (%)	5 (20.8)
Last EDSS scores before death	8.0 (3.0–9.5)
Spinal MRI lesion localization	
Cervical, *n* (%)[5]	17 (85.0)
Thoracic, *n* (%)[6]	12 (80.0)
Longitudinally extensive transverse myelitis[7]	18 (90.0)
Treatment for the prevention of relapse	
Immunosuppressant, *n* (%)	9 (37.5)
MMF	5 (20.8)
AZA	2 (8.3)
Other immunosuppressant use	2 (8.3)
Non-immunotherapy, *n* (%)	15 (62.5)

APS, area postrema syndrome; AQP4-Ab, aquaporin-4 antibody; ARR, annualized relapse rate; AZA, azathioprine; EDSS, Expanded Disability Status Scale; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TM, transverse myelitis; *n*, number; SD, standard deviation.

[1] A patient with unknown AQP4-Ab status.

[2] Two patients were excluded from the analysis because of monophasic disease durations.

[3] Four patients were excluded from the analysis because of disease durations ≤12 months.

[4] Three patients were excluded from the analysis due to death within 6 months of a severe motor attack.

[5] Four patients with unknown cervical MRI results.

[6] Nine patients with unknown thoracic MRI results.

[7] Four patients with unknown cervical or thoracic MRI results.

Table 3. Causes of death among the NMOSD patients in our study

Causes of death	Total (24) *N* (%)
Respiratory infection	11 (45.8)
Virus infection	2 (8.3)
Sepsis	2 (8.3)
Extensive cervical myelitis with respiratory failure	4 (16.7)
Suicide	2 (8.3)
Cervical cancer	1 (4.2)
Cerebral embolism	1 (4.2)
Unknown cause	1 (4.2)

NMOSD, neuromyelitis optica spectrum disorder; *n*, number.

all severely disabled patients were bedridden at home and their autoimmune function was decreased, increasing the risk of infection. Other common causes found in previous studies included respiratory failure[18] and sepsis while on immunosuppressive therapy.[19] Of the non-NMOSD-related deaths, the possible causes were cancer, pulmonary embolism, and cardiac infarction.[17]

In addition, 8.3% of the NMOSD patients died of suicide due to depression caused by severe attacks or sustained disability, deserving our attention. The number of investigations regarding depression in NMOSD patients is much smaller than those regarding depression in multiple sclerosis (MS) patients. Indeed, our previous study found that there was a large proportion of anxiety and depression in NMOSD patients. Anxiety and depressive symptoms were common in NMOSD patients, with high incidence rates of 68% and 25%, respectively.[20] In another study, patients with NMOSD were found to exhibit a similar prevalence (point prevalence 16%; lifetime prevalence 46%) of depression, and nearly half of the NMOSD patients in this study presented with recurrent depression and suicidality.[21] Concerns about depression in NMOSD patients should elicit the attention of neurologists to reduce the occurrence of such incidents. Eliasen et al. found that 9 out of 10 chronic neurological diseases, including MS, were associated with an increased risk of attempted suicide.[22] Concerns about suicidality are well established in the MS literature.[23–25] However, Moore et al. showed that suicide risk was higher in patients with NMOSD (41%) than in patients with MS (5%).[21] This finding was in accordance with another study by Fernández et al.[26] Thus, suicide-related mortality among NMOSD patients is an issue of particular concern. We should not only closely monitor visual or motor symptoms but also pay attention to mood disorders to avoid the occurrence of suicide.

The median survival time from symptom onset to death was 3.4 years, which was shorter than those in

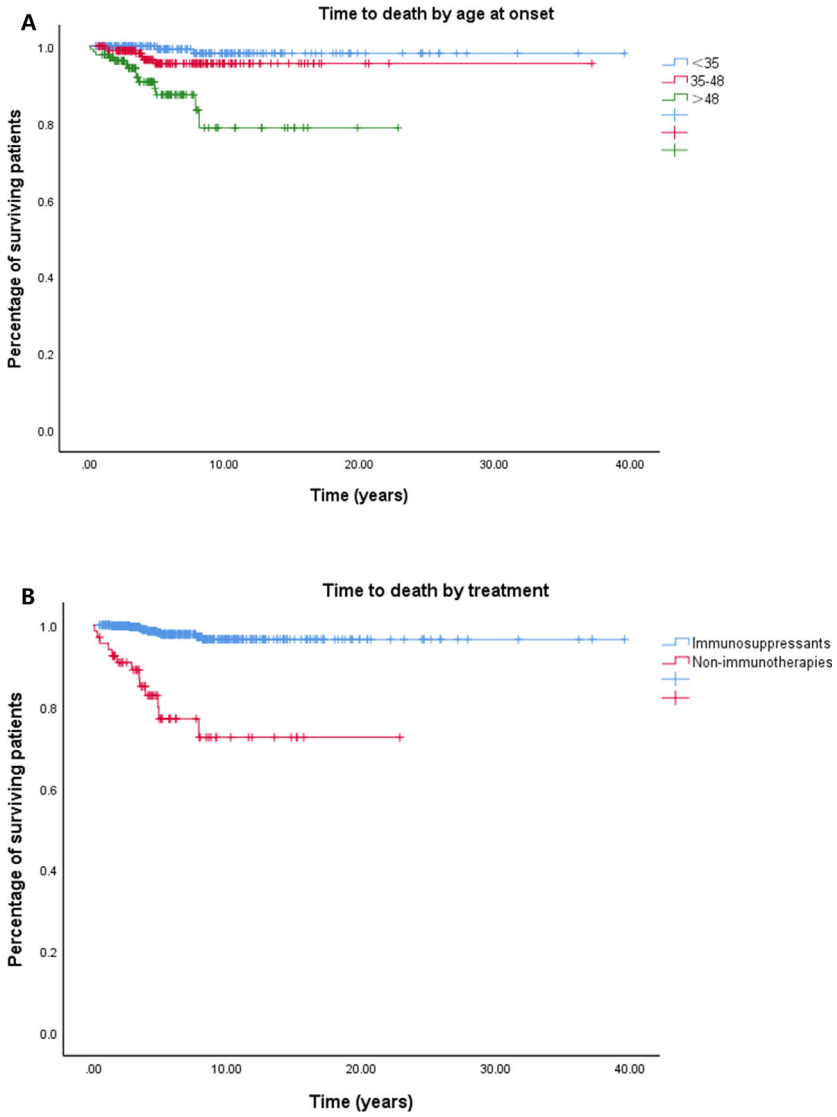

Figure 2. (A) Kaplan–Meier survival curve of the NMOSD patients by age at onset; (B) Kaplan–Meier survival curve of the NMOSD patients by treatment.

other studies that reported median survival times ranging from 6.9 to 17.0 years.[10,17–19,27] The following reason might explain the discrepancy. It has been indicated that older age at onset is a strong predictive factor for decreased survival time in patients with NMOSD.[17,19] The median age at onset (53.3 years old) of the deceased NMOSD patients in the current study was older than in other studies (23.5–45.4 years old).[10,17,18,27]

Our current data reveal prognostic factors for NMOSD-related mortality. Cox proportional hazard models were constructed to identify potential predictors of death. According to the results, older age at onset and a short first interattack interval were independent risk factors for mortality; these results were consistent with findings by Collongues et al.[19] and Cabre et al.,[18] respectively. A large multicenter cohort study also found that older age at onset was strongly predictive of death.[17] However, no significant association of sex, type of onset attack, onset attack severity, ARR, disability, or autoimmune comorbidity with death were found in this study. Wingerchuk et al. previously demonstrated that autoimmune comorbidities were associated with an increased risk of death in NMOSD patients.[27] Additionally, Collongues et al.[19] and Cabre et al.[18] found that high ARR and blindness at onset, respectively, were independently correlated with a shorter time to death in NMOSD

Table 4. Predictors of death in patients with NMOSD according to univariate and multivariable Cox proportional hazards models

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*p*-values	HR (95% CI)	*p*-values
Sex, male	2.66 (0.98–7.22)	0.055		0.061
Age at onset, every additional decade	2.39 (1.74–3.30)	<0.001	2.59 (1.74–3.86)	<0.001*
Phenotypes at onset				
ON	0.68 (0.29–1.62)	0.385		
TM	1.08 (0.46–2.54)	0.853		
APS	1.15 (0.39–3.41)	0.798		
Severe attack at onset				
ON	0.91 (0.34–2.47)	0.857		
TM	1.36 (0.56–3.34)	0.501		
Severe attack during the disease course				
ON	0.66 (0.28–1.58)	0.349		
TM	3.89 (1.15–13.16)	0.029		0.740
Time to the second attack	0.94 (0.90–0.99)	0.019	0.93 (0.89–0.98)	0.003*
ARR	0.37 (0.10–1.33)	0.128		
Visual disability before death	1.30 (0.51–3.34)	0.585		
Motor disability before death	8.15 (3.25–20.44)	<0.001		0.075
Autoimmune comorbidity	0.90 (0.35–2.30)	0.824		
Lack of regular immunotherapy	11.26 (4.81–26.40)	<0.001	10.34 (4.05–26.37)	<0.001*

ARR, annualized relapse rate; CI, confidence interval; HR, hazard ratio; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TM, transverse myelitis.

*p-value <0.05 by multivariable Cox proportional hazards model.

patients. Kitley et al. and Mealy et al. found that ethnicity was a risk factor for mortality in NMOSD patients.[10,17] These controversial results could be explained by these studies including different populations, and additional studies with longer follow-up periods and larger sample sizes are needed to further verify these results.

The overall mortality in the current study was 4.2% (24 of 596 patients), which is comparable to that in contemporary studies (3.3%–13%).[10,11,18,19] and considerably improved from older landmark studies (22%–32%).[17,27,28] This outcome might partly reflect increased awareness of the condition and thus early diagnosis and treatment. The decrease in mortality over time might also be the result of improved treatment options, including the use of high-dose methylprednisolone or plasmapheresis for acute attacks, as well as preventive immunotherapy during the remission stage. In addition, the help and support of medical personnel are also possible explanations. Additionally, it is vital to note that the definition of NMOSD has been revised over the past two decades, allowing for milder cases to be diagnosed. Similarly, testing for AQP4-Ab, which largely contributes to the laboratory differentiation of NMO and classical MS and can thus guide treatment decisions, became available in only the middle of the last decade. Thus, the decreased mortality could also be related in part to a technical artifact. Finally, genetic factors might also play a role since Asian populations appear to have a lower risk of relapse and disability than Caucasian populations; thus, they have a lower mortality rate.[17,29] In addition, patients of African origin were found to have significantly increased mortality compared to Caucasians and Asians.[10]

Our study had several limitations. Our study was a single-center observational study of patients mainly from Southwest China, and regional restrictions might limit the representative and universal applicability of our results. Only patients of Asian origin were included; thus, the results cannot be generalized to NMOSD worldwide. In addition, 73 patients lost to follow-up might have died, which would have affected the results. Most of the patients in our center were treated with immunosuppressants to prevent relapse, presumably resulting in low mortality among the detected cases and thus a relatively small sample size; some significant data might be missing. Additional studies with longer follow-up periods and larger sample sizes are therefore warranted to confirm our findings.

Conclusions

In our study, older age at onset, a short first interattack interval, and a lack of regular immunotherapy were significant predictors of mortality in NMOSD patients. Importantly, our results suggest that patients diagnosed with NMOSD should be treated with immunosuppressants as early as possible to decrease the risk of death.

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Author Contributions

H.Z. contributed to the conception and design of the study; Z.S., H.C., Y.Z., J.W., Y. Q., Z.Z., and Q.Z. contributed to the acquisition of the data. Q.D. contributed to drafting the text and preparing the tables and figures.

Conflict of Interest

Nothing to report.

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