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Acute transverse myelitis in demyelinating diseases among the Chinese

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Abstract The aim of the study was to characterize the demographic, clinical, and prognostic features of Chinese patients with acute transverse myelitis (ATM). The clinical data from ATM patients in a demyelinating disease database were analyzed retrospectively. Sixty-seven ATM patients with a follow-up duration longer than 2 years were identified. The frequency of neuromyelitis optica-related ATM (NMO-ATM) was high in our cohort (40.3%). Recurrent ATM (R-ATM), with a female predominance, was common in total idiopathic ATM (69.0%, 20/29). In R-ATM with longitudinally extensive spinal cord lesions (LESCLs), the high seropositivity of NMO-IgG, spinal cord lesions mostly involved the central gray matter and severer long-term disability were similar to NMO-ATM. In RTM without LESCLs, low seropositivity of NMO-IgG, preferentially involvement of the peripheral white matter and relative better neurological recovery were consistent with multiple sclerosis-related ATM (MS-ATM). The transition rates to MS in patients with acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM) were not significant (16.7 vs. 6.3%, $P = 0.753$), while LESCLs (OR = 11.4, $P = 0.028$) were significantly correlated with transition to NMO. The presence of LESCLs was the only variable showing a higher risk for reaching Rankin 3 (hazard ratio: 2.5, 95% CI: 1.0–6.1). Chinese patients with ATM had demographic, clinical, and prognostic features different from those in Western populations. Idiopathic R-ATM, common in Chinese, is a heterogeneous entity that shares partial clinical, spinal MRI and prognostic features with MS-ATM and NMO-ATM. The length of spinal cord lesion, rather than APTM/ACTM, may be a prognostic factor associated with clinical outcome and long-term disability in our population.

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Introduction

Acute transverse myelitis (ATM) is an inflammatory spinal cord disorder that has a variety of clinical manifestations, although the details of its pathogenesis are unknown in many cases [1]. There are several subtypes of ATM, such as those associated with multiple sclerosis (MS) [2], neuromyelitis optica (NMO) [3], systemic autoimmune disease [4], infection [5, 6], as well as cases with no specific origin (idiopathic ATM) [7]. Although ATM has been widely studied in the Caucasian population, the demographic, clinical, and prognostic features of ATM in Asian populations such as the Chinese have been rarely reported, and it is unclear whether they are distinct from those in Western patients. Therefore, a comprehensive evaluation of ATM in the Chinese, and in particular identification of clinical outcomes in the early stages of the disease, is particularly important for early clinical diagnosis, prognosis, and treatment.

Methods

Patients and classification

The MS Center of the Third Affiliated Hospital of Sun Yat-Sen University is one of the largest referral centers for MS and other demyelinating diseases in Southern China [8]. Potential ATM cases were identified by querying the patient database from January 1, 1995 to October 31, 2009 for a final diagnosis of myelopathy, myelitis, MS, or NMO. Patients were enrolled in the study if they fulfilled the inclusion and exclusion criteria for ATM proposed by the Transverse Myelitis Consortium Working Group (2002) [1]. In addition, all subjects must have had at least one follow-up visit at our Center more than 2 years after the onset of symptoms. Fulfillment of the inclusion and exclusion criteria was confirmed retrospectively by a review of medical records by two neurologists specialized in the demyelinating diseases (Xueqiang HU and Wei QIU).

ATM was subclassified as: (1) MS-related ATM (MS-ATM): patients with a diagnosis of definite MS [9]; (2) NMO-related ATM (NMO-ATM): patients with a diagnosis of NMO [10] (the 1999 Wingerchuk diagnostic criteria [3] was used for several cases due to the lack of NMO-IgG data); (3) systemic disease-related ATM (SD-ATM): patients with clinical evidence of systemic diseases; (4) infectious ATM: patients with serologic evidence of infection with, for example, herpes simplex virus (HSV) or varicella zoster virus (VZV); (5) monophasic ATM (M-ATM): patients with idiopathic ATM without relapses; (6) recurrent ATM (R-ATM): patients with idiopathic ATM who had suffered relapses, but without clinical evidence to permit a diagnosis of MS or NMO.

Based on the clinical and magnetic resonance imaging (MRI) findings, ATM patients were classified as having acute complete transverse myelitis (ACTM) or acute partial transverse myelitis (APTM) according to the definition by Scott et al. [11]. Longitudinal extensive spinal cord lesions (LESCLs) was defined as spinal cord lesions extending over three or more vertebral segments on spinal cord MRI [12]. Holocord lesion was defined as a spinal lesion occupying more than two-thirds of the cross-sectional area of the cord.

Clinical data

The patients' medical records were reviewed retrospectively, and the following data were retrieved: gender, age at onset, disease duration, number of relapses, Modified Rankin Scale [13] at last visit, clinical manifestations, laboratory and MRI findings, and therapy including use of methylprednisolone, interferon-beta (INF-β), and/or immunosuppressants.

Laboratory tests

Systemic disease screening tests were performed as routine in most cases, including for anti-SSA/SSB antibody, anti-nuclear antibody, anti-dsDNA antibody, anti-sm antibody, anti-RNP antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, and serology for infectious ATM such as antibodies to HSV-1, HSV-2, and VZV. Serum NMO-IgG antibodies were tested using aquaporin 4-transfected cells from a commercial sampling kit (EUROIMMUN AG, Lübeck, Germany) according to the manufacturer's instructions. The sensitivity and specificity of NMO-IgG by this method for NMO patients in our cohort was 84.0 and 85.0%, respectively [8].

MRI scanning

All MRI scans were performed on a GE 1.5 T MR imager scanner (General Electric, Milwaukee, WI) in the Radiology Department of the Third Affiliated Hospital of Sun Yat-Sen University. The slice thickness of the axial scans ranged from 3–5 mm. The imaging parameters for the spinal cord MRI were as follows: T1 with and without gadolinium enhancement (400/15.5 ms, TR/TE), and T2 (2,500–3,500/100 ms, TR/TE). Most brain MRI scans were performed using T1, T2, proton density, and fluid attenuated inversion recovery (8,800–/120 ms, TR/TE) sequences.

Statistical analysis

Differences between the groups were assessed using analysis of variance, the 2-tailed t test, the Mann–Whitney test, or the Kruskal–Wallis test for quantitative variables, and the chi-squared test or Fisher's exact test for categorical variables. Kaplan–Meier survival analysis was used for time-dependent outcomes, and differences between the survival curves were analyzed using the log-rank test. The correlation between categorical variables and outcomes was analyzed by the Cox regression test. P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 16.0 (Microsoft Corporation, San Francisco CA).

Results

Demographic features

Our database comprised 282 patients with demyelinating diseases who were diagnosed and managed from 1995 to 2009 in our MS center. As shown in Fig. 1, there were 67 ATM patients with a follow-up duration longer than 2 years finally enrolled in this study. Forty-four (65.7%)
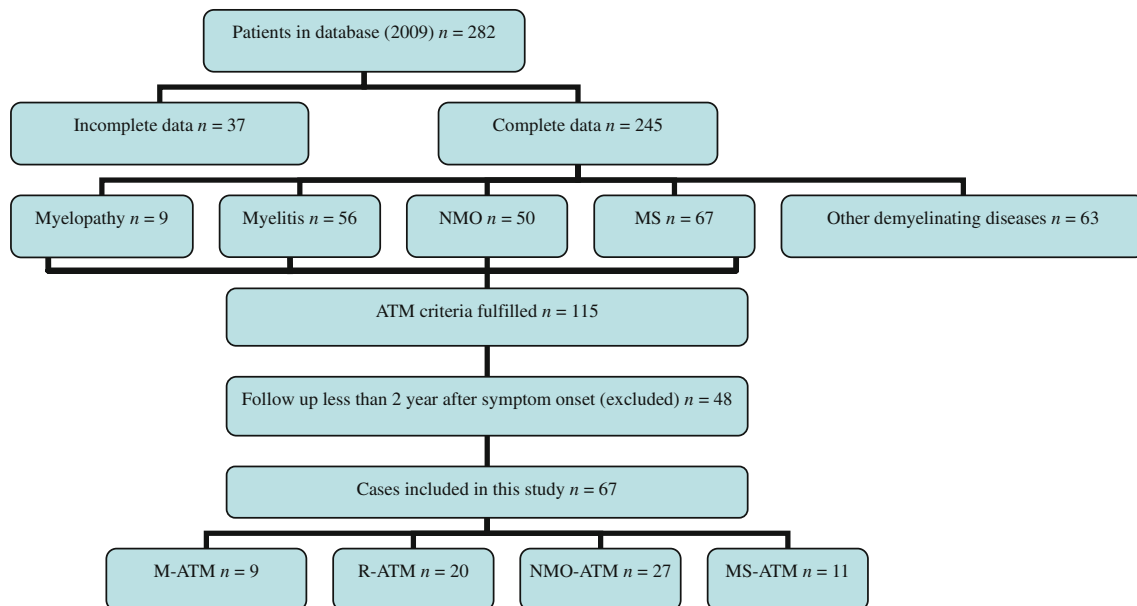
Fig. 1 Patient selection flow chart. *MS* Multiple sclerosis, *NMO* neuromyelitis optica, *R-ATM* recurrent transverse myelitis, *ATM* acute transverse myelitis

patients had the onset syndrome of ATM, and the other 23 (34.3%) patients were diagnosed during the disease course. Classification of ATM in our cohort was compared with that in other studies (Table 1). The proportion of NMO-ATM was markedly higher than that reported in western populations (40.3 vs. 0–27.1%). Interestingly, no cases with infectious ATM or SD-ATM were found in our cohort. All patients with ATM received intravenous methylprednisolone pulse therapy (1,000 mg/day for 3–5 days) in the acute phase. Immunosuppressants were used in 16 patients in the acute phase. INF-β was used in six patients in remission.

Clinical and laboratory findings

The clinical characteristics of the ATM subgroups are shown in Table 2. Male and elderly patients were more common than expected in the M-ATM group, but not in the R-ATM, NMO-ATM, or MS-ATM groups. Peak onset age was 40s in M-ATM, and 30s in R-ATM. R-ATM with LESCLs had a high positivity of NMO-IgG (75.0%) and poor long-term disability (54.5% in moderate or severe disability) which was comparable with NMO-ATM (90.0% NMO-IgG positive rate, and 48.1% in moderate or severe disability). Low seropositive rate of NMO-IgG (0) and relative better neurological recovery (11.1% in moderate or severe disability) in RTM without LESCLs were similar to those in MS-ATM (10.0% NMO-IgG positivity, and 18.2% in moderate or severe disability).

MRI features

Spinal cord MRI was undertaken in 45 ATM patients in the acute stage and 22 ATM patients in the remitting stage. One of 9 (11.1%) M-ATM and 15.0% (3/20) R-ATM had holocord lesions. Spinal cord lesions in the R-ATM without LESCLs group (66.7%), and the MS-ATM group (72.7%) mostly involved the peripheral white matter in the cervical cord (Table 2) (Fig. 2a, b). Spinal cord lesions in RTM with LESCLs (54.5%) and NMO-ATM group (63.0%) mostly involved the central gray matter (Fig. 2c).

Prognosis in ATM patients

Forty-four (65.7%) in a total of 67 patients had ATM as initial symptom. All of these 44 patients were followed up at least 2 years after their first episode of ATM: 20.5% (9/44) of patients did not show a second episode of neuroinflammation during the follow-up period; 45.5% (20/44) patients suffered relapses; 22.7% (10/44) developed NMO; 11.4% (5/44) converted to MS. The variables associated with conversion to NMO and MS are shown in Tables 3 and 4, respectively. Seropositivity for NMO-IgG (odds ratio (OR) = 15.4, $P = 0.019$) and the presence of LESCLs (OR = 11.4, $P = 0.028$) were significantly correlated with transition to NMO. Brain lesions fulfilling Barkhof criteria for MS increased risk for developing to MS ($P = 0.001$). There is not significant difference in the

Table 1 Comparison of ATM patients and clinical subgroups among studies

	Patients n (m/f)	Period of follow-up	Age range, years	I-ATM n (%)	I-ATM n (%)	SD-ATM n (%)	NMO-ATM n (%)	MS-ATM n (%)	Myelopathy n (%)
Alvarenga, [7]	70 (NR)	2000–2008	NR	41 (58.6)	5 (7.1)	2 (2.9)	19 (27.1)	2 (2.9)	1 (1.4)
J. de Seze, [17]	288 (NR)	1994–2004	NR	45 (15.6)	50 (17.4)	59 (20.5)	49 (17.0)	31 (10.8)	54 (18.8)
Michael Harzheim, [15]	45 (10/35)	1997–2000	17–72	16 (35.6)	17 (37.8)	2 (4.4)	0	10 (22.2)	0[a]
J. de Seze, [14]	79 (26/53)	1994–1999	19–78	39 (49.4)	5 (6.3)	13 (16.5)	0	34 (43.0)	14 (17.7)
Our data	67 (14/53)	1995–2009	14–80	29 (43.3)	0	0	27 (40.3)	11 (16.4)	0[a]

IATM Idiopathic acute transverse myelitis, *I-ATM* infectious acute transverse myelitis, *SD-ATM* systemic disease-related acute transverse myelitis, *NMO-ATM* neuromyelitis optica-related acute transverse myelitis, *MS-ATM* multiple sclerosis related acute transverse myelitis, *NR* not reported

[a] Myelopathy was not included in these studies

Table 2 Comparison of clinical and MRI findings among ATM subgroups according to the presence or absence of LESCLs

	M-ATM ($n = 9$)	R-ATM ($n = 20$)		NMO-ATM ($n = 27$)	MS-ATM ($n = 11$)
		LESCLs − $n = 9$	LESCLs + $n = 11$		
Sex ratio, F:M	4:5	6:3	10:1	24:3	9:2
Age of onset, mean (SD), years	43.3 (18.7)	36.0 (10.1)	35.2 (10.7)	34.9 (15.1)	28.2 (9.8)
Follow-up period, median (range), months	59 (24–106)	36 (24–120)	36 (25–176)	49 (24–124)	48 (24–156)
ACTM, n (%)	0 (0)	3/9 (33.3)	7/11 (63.6)	11/27 (40.7)	1/11 (9.1)
CSF pleocytosis, n (%)	3/9 (33.3)	2/7 (28.6)	5/10 (50.0)	6/22 (27.3)	3/11 (27.3)
NMO-IgG-positive, n (%)	0 (0)	0 (0)	6/8 (75.0)	18/20 (90.0)	1/10 (10.0)
Rankin score at last visit, median (range)	0 (0–4)	1 (1–5)	3 (0–5)	2 (0–6)	2 (0–4)
Moderate or severe disability, n (%)[a]	2/9 (22.2)	1/9 (11.1)	6/11 (54.5)	13/27 (48.1)	2/11 (18.2)
Number of relapses, median (range)	0	2 (0–5)	3 (1–15)	2 (0–12)	2 (0–15)
Spinal MRI					
Cervical cord, n (%)	5/9 (55.6)	6/9 (66.7)	8/11 (72.7)	20/27 (74.1)	8/11 (72.7)
Thoracic cord, n (%)	6/9 (66.7)	3/9 (33.3)	9/11 (81.8)	20/27 (74.1)	6/11 (54.5)
Holocord lesions, n (%)	1/9 (11.1)	0 (0)	3/11 (27.3)	7/27 (25.9)	1/11 (9.1)
Peripheral lesions, n (%)	4/9 (44.4)	6/9 (66.7)	2/11 (18.2)	3/27 (11.1)	7/11 (63.6)
Central lesions, n (%)	4/9 (44.4)	3/9 (33.3)	6/11 (54.5)	17/27 (63.0)	3/11 (27.3)
LESCLs, n (%)	4/9 (44.4)	0 (0)	11/11 (100.0)	18/27 (66.7)	2/11 (18.1)
Brain lesions fulfilling Barkhof criteria for MS, n (%)	1/5 (20.0)	0 (0)	0 (0)	3/19 (15.8)	8/11 (72.7)

MRI Magnetic resonance imaging, *LESCLs* longitudinal extensive spinal cord lesions, *M-ATM* monophasic acute transverse myelitis, *R-ATM* recurrent acute transverse myelitis, *NMO-ATM* neuromyelitis optica-related acute transverse myelitis, *F* female, *M* male, *ACTM* acute complete transverse myelitis, *CSF* cerebrospinal fluid

[a] Rankin 3–6

transition rates to MS in patients with APTM and ACTM (16.7 vs. 6.3%, $P = 0.753$).

With regard to the disability, 14.9% (10/67) of patients made a full recovery (Rankin 0), 49.3% (33/67) had mild disability (Rankin 1–2), 19.4% (13/67) showed moderate disability (Rankin 3), and 16.4% (11/67) had severe disability (Rankin 4–6). Cox regression analysis was performed to investigate the factors (gender, age of onset, disease duration, ACTM, LESCLs, >1 spinal lesion, number of relapses, INF-β therapy) associated with reaching Rankin 3. The presence of LESCLs was the only variable showing a higher risk for reaching Rankin 3 (hazard ratio: 2.5, 95% CI: 1.0–6.1), and this risk was independent of the other variables (Table 5). Kaplan–Meier survival analysis showed that patients with LESCLs reached Rankin 3 faster than patients without LESCLs (7.5 vs. 10.5 years; log rank 5.1, $P = 0.024$) (Fig. 3). Moreover, the frequency of moderate or severe disability in

patients with LESCLs was significantly higher than in those without LESCLs (17/35 vs. 7/32, OR = 3.4, $P = 0.023$).

Discussion

ATM is a clinical spectrum with heterogeneous etiologies. Clinical data from Chinese ATM patients is scarce. To our knowledge, this is the first study to investigate the demographic features, characteristics, and prognostic factors of ATM, including idiopathic and disease-related ATM, in the Chinese population.

The relative proportions of the different ATM subgroups in Asians were not well established. In our study, the proportion of NMO-ATM was markedly higher than that reported in the western populations [7, 14–17] and there were no cases of infectious ATM or SD-ATM. This may reflect the high prevalence of NMO in Asians. However, we should consider that selection bias caused by limited laboratory testing for infectious ATM may skew the data.

It has been reported that idiopathic ATM can affect any age, but has bimodal peaks between 10 and 19 years and between 30 and 39 years, with no sex predisposition [1, 18], and that the monophasic form (M-ATM) constitutes the majority of cases [19–22]. Idiopathic ATM on MRI is characterized by a centrally located high T2 signal lesion occupying more than two-thirds of the cross-sectional area of the cord, greater than three vertebral segments in length, with a predilection for the thoracolumbar cord [23, 24]. The present study showed some deviations from these reports in the clinical profiles of Chinese patients with idiopathic ATM: (1) M-ATM was found in only 31.0% (9/29) of idiopathic ATM patients, while R-ATM was common (69.0%, 20/29); (2) there was no peak age of onset between 10 and 19 years; (3) female predominance in R-ATM was different from other reports [25–27]; (4) spinal lesions occupying more than two-thirds of the cross-sectional area of the cord were rare, and only 11.1% (1/9) M-ATM patients and 15.0% (3/20) R-ATM had holocord lesions.

R-ATM has been referred to MS [14, 28], spinal cord-restricted NMO [29], or systemic disease [14], and only a small series of idiopathic R-ATM has been previously reported [25, 30, 31]. Three western studies reported that idiopathic R-ATM was different from classical MS [25, 27, 32], and recurrent longitudinal extensive myelitis (RLEM), with high serum positive rate for NMO-IgG antibodies was included in the NMO spectrum [29]. In contrast, in Asia, idiopathic R-ATM without extra-spinal lesions may be

Fig. 2 Sagittal (*upper*) and axial (*lower*) distributions of spinal cord lesions in ATM subgroups. **a** Spinal cord lesion in an R-ATM patient without LESCLs that involved the peripheral cord. **b** Spinal cord lesion in an MS-ATM patient without LESCLs that involved the peripheral cord. **c** Spinal cord lesion in an NMO-ATM patient that involved the central cord. The lesions are shown by arrows. *ATM* Acute transverse myelitis, *R-ATM* recurrent ATM, *LESCLs* longitudinal extensive spinal cord lesions, *MS-ATM* multiple sclerosis related ATM, *NMO-ATM* neuromyelitis optica related ATM

Table 3 Variables associated with conversion to NMO

	No. (%) of cases		OR (95% CI) of conversion to NMO	P value
	Conversion to NMO	No conversion to NMO		
LESCLs +	9 (37.5)	15 (62.5)	11.4 (1.3–100.3)	0.028
LESCLs −	1 (5.0)	19 (95.0)		
ACTM	5 (31.2)	11 (68.8)	NA	0.518
APTM	5 (17.9)	23 (82.1)		
NMO-IgG +	9 (56.3)	7 (43.7)	15.4 (1.6–148.8)	0.019
NMO-IgG −	1 (7.7)	12 (92.3)		

LESCLs Longtitudinal extensive spinal cors lesions, *ACTM* acute completed transverse myelitis, *APTM* acute partial transverse myelitis, *NA* not analyzed as $P > 0.05$

Table 4 Variables associated with conversion to MS

	No. (%) of cases		OR (95% CI) of conversion to MS	P value
	Conversion to MS	No conversion to MS		
LESCLs −	5 (25.0)	15 (75.0)	NA*	0.014
LESCLs +	0 (0)	24 (100.0)		
APTM	4 (16.7)	24 (85.7)	NA	0.753
ACTM	1 (6.3)	15 (93.7)		
Barkhof lesions +	5 (62.5)	3 (37.5)	NA*	0.001
Barkhof lesions −	0 (0)	17 (100.0)		

LESCLs Longtitudinal extensive spinal cord lesions, *ACTM* acute completed transverse myelitis, *APTM* acute partial transverse myelitis, *Barkhof lesions* brain lesions fulfilling Barkhof criteria for MS, *NA* not analyzed as P > 0.05, *NA** not analyzed as the value of one weight variable was zero

Table 5 Univariate and multivariate Cox regression analysis of the risk of reaching an Rankin score of 3.0

	Univariate Cox analysis				Multivariate Cox analysis			
		95% CI				95% CI		
	HR	Lower	Upper	P value	HR	Lower	Upper	P value
Gender	0.8	0.3	2.3	0.677	NA			
Age at onset	1.0	1.0	1.1	0.001	NA			
Disease duration	1.0	1.0	1.0	0.106	NA			
ACTM	1.6	0.7	3.7	0.235	1.6	0.7	3.5	0.289
LESCLs	2.6	1.1	6.2	0.035	2.5	1.0	6.1	0.040
>1 spinal lesion	1.0	0.4	2.3	0.981	NA			
Number of relapses	1.0	0.9	1.1	0.950	NA			
INF-β in remission	1.2	0.4	4.1	0.742	NA			

CI confidence interval, *HR* hazard ratio, *NA* not analyzed, *ACTM* acute complete transverse myelitis, *LESCLs* longitudinal extensive spinal cord lesions, *INF-β* interferon-beta

considered as spinal MS [33], and RLEM was different from spinal-restricted NMO [26, 34]. Therefore, the nosology of idiopathic R-ATM remains controversial. We speculate that idiopathic R-ATM, common in Chinese, is a heterogeneous entity that shares partial clinical, spinal MRI and prognostic features with MS-ATM and NMO-ATM. This conclusion was corroborated by : (1) In R-ATM with LESCLs, the high seropositivity rate of NMO-IgG, spinal cord lesions mostly involved the central gray matter and severer long-term disability were similar to NMO [12, 35]. It supported the western report that RLEM should be included in the NMO spectrum [29]; (2) Contrary to some clinical findings in the western reports [25, 27, 32], we did not find factors to differentiate RTM without LESCLs from MS-ATM, except of the onset age and frequency of Barkhof Brain lesions. Female predominance, low sero-positivity of NMO-IgG, preferentially involvement of the peripheral white matter in cervical cord and relative better neurological recovery in these patients were consistent with MS-ATM. Some patients had multiple silent brain lesions. Therefore, we suspect that these R-ATM without LESCLs in our study most likely suffered from a unique inflammatory demyelinating disorder within MS but restricted to the spinal cord, though not fulfilling the Barkhof criteria.

The rate of transition to NMO after first-episode ATM has been reported to be low in Western countries (<1%) [36, 37]. However, a study from Hong Kong reported a higher rate of 9.4% [34]. Our findings were even higher than the latter, at 22.7%. In addition, we confirmed that seropositivity for NMO-IgG is predictive of subsequent conversion to NMO, while ATM with Barkhof brain lesions [38, 39] confers a high risk for conversion to MS.

According to some western reports, APTM/ACTM is somewhat related to the clinical outcomes of patients with an initial presentation of ATM [11, 36, 40–42]. Scott et al. [11] suggested that it may be beneficial to develop criteria for both APTM and ACTM. Their report did not focus on
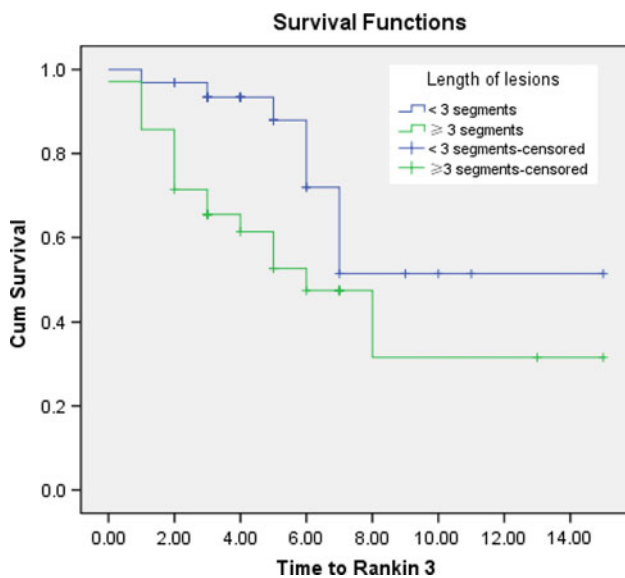
Survival Functions

Fig. 3 Kaplan–Meier survival analysis of the time to reach Rankin 3.0 according the length of the spinal cord lesions

the length of the spinal lesion on MRI as a potentially important feature of prognosis in ATM patients, although it did mention that the spinal lesions of APTM on MRI tend to be smaller than those of ACTM; those of the latter generally extend over multiple cord levels. Our study suggests that the length of spinal cord lesion, rather than APTM/ACTM, may be a prognostic factor associated with clinical outcome and long-term disability. We did not confirm that APTM was associated with an increased risk of conversion to MS [11, 36, 40–42]. Interestingly, LESCLs were correlated with a higher risk of conversion to NMO (OR = 11.4, $P = 0.028$), and more ATM patients without LESCLs developed to MS ($P = 0.014$). In addition, the presence of LESCLs was the only prognostic factor associated with severer long-term disability in ATM patients. The fact that the length of the spinal cord lesions was more strongly correlated with clinical outcomes and long-term disability than APTM/ACTM implies that the classification of APTM and ACTM by Scott et al. [11] may be inappropriate for the Chinese population. We found a few APTM patients with LESCLs in our study, contrary to Western reports on APTM with smaller spinal cord lesions. It may partially explain the difference. A larger study with a longer follow-up period will be helpful in answering this question.

In conclusion, Chinese patients with ATM had demographic, clinical, and prognostic features different from those in Western populations. Idiopathic R-ATM, common in Chinese, is a heterogeneous entity that shares partial clinical, spinal MRI and prognostic features with MS-ATM and NMO-ATM. The length of spinal cord lesion, rather than APTM/ACTM, may be a prognostic factor associated with clinical outcome and long-term disability in our population.

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