



# Clinical, laboratory features, and prognostic factors in adult acute transverse myelitis: an Italian multicenter study

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## Abstract

**Objectives** We compared the clinical, laboratory, and radiological features of different subgroups of acute transverse myelitis (ATM) diagnosed according to the criteria established by the Transverse Myelitis Consortium Working Group (TMCWG) as well as of non-inflammatory acute transverse myelopathies (NIATM) to identify possible short- and long-term prognostic factors.

**Methods** A multicenter and retrospective study comprising 110 patients with ATM and 15 NIATM admitted to five Italian neurological units between January 2010 and December 2014 was carried out.

**Results** A significantly higher frequency of isolated sensory disturbances at onset in ATM than in NIATM patients (chi-square = 14.7;  $P = 0.005$ ) and a significantly higher frequency of motor symptoms in NIATM than ATM (chi-square = 12.4;  $P = 0.014$ ) was found. ATM patients with high disability at discharge had more motor-sensory symptoms without (OR = 3.87;  $P = 0.04$ ) and with sphincter dysfunction at onset (OR = 7.4;  $P = 0.0009$ ) compared to those with low disability. Higher age (OR = 1.08;  $P = 0.001$ ) and motor-sensory-sphincter involvement at onset (OR = 9.52;  $P = 0.002$ ) were significantly associated with a high disability score at discharge and after a median 1-year follow-up.

**Conclusions** The diagnosis of ATM may prevail respect to that of NIATM when a sensory symptomatology at onset occurs. In ATM, patients older and with motor-sensory involvement with or without sphincter impairment at admission could experience a major risk of poor prognosis both at discharge and at longer time requiring a timely and more appropriate treatment.

**Keywords** Transverse myelitis · Neuromyelitis optica spectrum disorders · Multiple sclerosis · Connective autoimmune disorders · Disability · Prognosis

## Introduction

Acute transverse myelitis (ATM) is an acute inflammatory neurological disorder of the spinal cord causing bilateral

complete or partial motor and/or sensory impairment with or without sphincter dysfunction and showing heterogeneous etio-pathogenesis with different outcomes (reviewed in [1]). Prior to the establishment of diagnostic criteria of ATM

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defined by the Transverse Myelitis Consortium Working Group (TMCWG) [2], the literature on this topic was almost confusing consisting mainly of single-center studies recruiting small heterogeneous cohorts often including non-inflammatory acute myelopathies (AM) and with incomplete work-up regarding laboratory, neurophysiological as well as brain and spinal cord neuroradiological assessment [3–5]. The TMCWG criteria have led to distinction between idiopathic and disease-associated ATM including myelitis occurring in the course of autoimmune diseases also defining the “possible” ATM type when clear inflammatory signs at the cerebrospinal fluid (CSF) analysis or at magnetic resonance imaging (MRI) are lacking despite the presence of defined clinical features [2]. A further advance in approaching the etiology and clinical pattern of ATM has been achieved with the identification of neuromyelitis optica (NMO)-IgG antibody binding to aquaporin-4 (AQP4) as laboratory biomarker of the NMO spectrum disorders (NMOSD) [6]. However, there are a few studies on AM including in the diagnostic work-up search for serum NMO-IgG [7, 8] and, to the best of our knowledge, only a few studies on idiopathic ATM defined according to the TMCWG criteria but not including serum NMO-IgG assay were carried out [9, 10]. Need for a rapid diagnosis to establish a correct treatment requires identification of clinical and laboratory features allowing to differentiate inflammatory ATM from AM with vascular, metabolic, paraneoplastic, and neoplastic etiology. In addition, as ATM is a neurological disorder with different clinical outcomes characterized by complete recovery or persistence of mild or severe disability [4, 11–14], the identification of factors useful for establishing short- and long-term prognosis based on the TMCWG diagnostic criteria still remains a challenge. To address these issues, we designed a multicenter retrospective study aimed to compare the clinical, laboratory, and radiological features of idiopathic, disease-associated and possible ATM as well as of all ATM with respect to non-inflammatory acute transverse myelopathies (NIATM) as control group. In addition, we attempted to identify possible short- and long-term prognostic factors in ATM.

## Patients and methods

### Patients

This study was observational and retrospective comprising 125 patients with inflammatory ATM and NIATM selected from all myelopathies admitted to five Italian neurological units (two from northern, two from central, and one from southern Italy) between January 2010 and December 2014. One hundred and ten ATM fulfilling the TMCWG criteria [2] were enrolled in the study and included 73 idiopathic, 29 disease-associated, and 8 possible ATM. The disease-

associated group included 3 Sjogren's syndromes, 6 parainfectious and post-vaccine myelitis, 12 multiple sclerosis, and 8 NMOSD [15]. NIATM included 15 patients (11 vascular, 2 compressive, 2 vitamin B12 deficiency), all with acute onset of symptoms not exceeding 21 days prior to admission that is the maximum time of progression to nadir considered by the TMCWG criteria. The baseline demographic and clinical characteristics of the cohorts are listed in Table 1. The diagnostic criteria and definitions of the different groups studied are summarized in the supplementary Table S1. Clinical and laboratory findings were obtained from clinical records in each center. Informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of the Medical School of the University of Siena (site of the coordinating center) and the local ethics boards of the other participating centers.

### Laboratory tests and neurophysiological examinations

Apart from routine laboratory tests, extended work-up for autoimmunity including anti-nuclear antibodies, anti-DNA antibody, and anti-SSA and anti-SSB antibodies was performed in all ATM patients. Serum anti-aquaporin-4 (AQP4) IgG was searched with commercial cell based assay (Euroimmun, Germany) in 74 of 110 (67.2%) ATM and in 6 of 15 (40%) NIATM. CSF analysis including protein level, cell count, and search for oligoclonal bands with isoelectric focusing was performed in all patients. CSF virological tests including polymerase chain reaction (PCR) for DNA of herpes simplex virus (HSV) -1 and -2, human herpes virus (HHV) -6, Epstein Barr virus (EBV), cytomegalovirus (CMV), and varicella zoster virus (VZV) were performed in 75 of 110 (68%) ATM and 12 of 15 (80%) NIATM.

Neurophysiological examinations including visual evoked potentials (VEPs), somatosensory evoked potentials (SSEPs), and motor-evoked potentials (MEPs) were performed in 83 of 110 (75.4%), 83 of 110 (75.4%), and 49 of 110 (44.5%) ATM, respectively, as well as in 1 of 15 (6.6%), 7 of 15 (46.7%), and 8 of 15 (53.3%) NIATM, respectively.

### MRI parameters

All patients underwent spinal cord MRI at 1.5 Tesla according to the standard procedures in each unit. Spinal cord MRI was performed in a median time from the disease onset of 4 days (IQR = 2–14). Brain MRI was performed in all ATM patients and in 8 of 15 (53%) NIATM. The number of T2-weighted and T1-weighted gadolinium-enhancing (GAD<sup>+</sup>) lesions in brain and spinal cord MRI was assessed. The number of segments on the sagittal plane involved in spinal cord MRI lesions was also estimated.

**Table 1** Baseline demographic and clinical characteristics of the cohorts at admission

	IATM ( <i>n</i> = 73)	DAATM ( <i>n</i> = 29)	PATM ( <i>n</i> = 8)	ATM (all) ( <i>n</i> = 110)	NIATM ( <i>n</i> = 15)	<i>P</i>
Gender (F/M)	42/31	24/5	7/1	73/37	7/8	n.d.
Age (years)	46.8 ± 2	44.7 ± 3	45 ± 5	46 ± 2	59 ± 5	0.03
Time to admission (days)	5 ± 0.7	11 ± 1.8	4 ± 1	7.9 ± 1	15.5 ± 10	0.06
Hospitalization (days)	24 ± 1.7	18 ± 3	14 ± 3	21.8 ± 1.4	20 ± 3.9	0.12
Rankin score at admission	2.2 ± 0.1	1.9 ± 0.2	2.6 ± 0.4	2.1 ± 0.1	3.5 ± 0.3	< 0.0001

*IATM*, idiopathic acute transverse myelitis; *DAATM*, disease-associated acute transverse myelitis; *PATM*, possible acute transverse myelitis; *NIATM*, non-inflammatory acute transverse myelopathies; *n*, number of subjects; *F/M*, females/males. *n.d.*, not determined. The results are shown as mean ± SEM. ANOVA with Tukey post test was used

## Clinical features, treatment, and outcome

The following clinical parameters were considered: time from disease onset to the admission, neurological symptoms/signs at onset, and duration of hospitalization. All ATM patients were treated with intravenous (IV) high-dose corticosteroids for 5 to 7 days. NIATM patients were treated with IV corticosteroids or anticoagulants including low-molecular-weight heparin or clopidogrel. Clinical outcome was estimated assessing disability with modified Rankin scale [16] both at the admission and at the discharge. Poor prognosis was established when a Rankin score  $\geq 3.0$  at the discharge was found. Clinical follow-up was available for 95 of 110 (86.4%) ATM patients and 3 of 15 (20%) NIATM.

## Statistical analysis

Comparison of continuous clinical parameters among idiopathic, disease-associated, and possible ATM was performed with ANOVA and Tukey post test, whereas for comparison of total ATM patients with NIATM group unpaired T test was used. Frequency of categorical variables was analyzed with the chi-square test for large contingency tables and Fisher's exact test for  $2 \times 2$  tables. Odds ratio (OR) and its 95% confidence interval (CI) were also calculated. To establish whether poor prognosis at the discharge could depend on the presence of other variables, multivariate analysis with stepwise logistic regression was performed taking as dependent variables disability score at the Rankin scale  $<$  or  $\geq 3.0$ . The independent variables were the following: age, time to admission, motor-sensory, motor-sensory-sphincter and sensory-pain presenting symptoms, number of spinal cord segments, and presence of CSF oligoclonal bands. All statistical tests were performed with GraphPad Prism 7.02 software, San Diego, CA, USA, except for stepwise logistic regression analysis performed with SPSS software package version 13.0 (SPSS Inc., Chicago, IL, USA). Values of  $P < 0.05$  were considered significant.

## Results

### Baseline clinical characteristics of the ATM subgroups and non-inflammatory ATM

There were no significant differences with regard to the time of symptoms onset to admission neither to duration of hospitalization among the groups. However, NIATM displayed a significantly higher age ( $P = 0.03$ ) as well as higher disability score at the admission than ATM patients ( $P < 0.0001$ ) (Table 1).

### Clinical symptoms and signs at onset of the ATM and NIATM patients

The frequency of neurological symptoms/signs at the disease onset is shown in Table 2. Clear sensory level was found in 102 of 110 (93%) ATM patients including all idiopathic and disease-associated patients (21.6% was cervical, 71.6% thoracic, and 6.8% lumbar) and in 9 of 15 (60%) NIATM patients including 7 vascular, 1 compressive and 1 vitamin B12 deficiency (67% was thoracic and 33% lumbar). There were no significant differences among ATM subgroups with regard to the frequency of any of neurological symptoms or signs at onset except for a higher frequency of motor-sensory symptoms in possible ATM patients compared to other subgroups ( $P = 0.0003$ ). However, significantly higher frequency of isolated sensory disturbances at onset in ATM subgroups as well as in all ATM than in NIATM patients (chi-square = 14.7;  $P = 0.005$ ) was found. Conversely, NIATM patients showed a significantly higher frequency of isolated motor symptoms than ATM subgroups (chi-square = 12.4;  $P = 0.014$ ).

### Laboratory findings of the ATM and NIATM patients

Serum AQP4 IgG was detected in 8 of 19 (42%) disease-associated but in none of the idiopathic or possible ATM patients (chi-square = 27.6;  $P < 0.0001$ ). AQP4-positive patients were diagnosed as having NMO (2 cases), relapsing and

**Table 2** Clinical symptoms and signs at onset of the cohorts

	IATM ( <i>n</i> = 73)	DAATM ( <i>n</i> = 29)	PATM ( <i>n</i> = 8)	ATM (all) ( <i>n</i> = 110)	NIATM ( <i>n</i> = 15)	Chi-square	<i>P</i>
Motor, <i>n</i> (%)	1/73 (1.3)*	3/29 (10)	0/8 (0)	4/110 (4)**	3/15 (20)	12.4	0.014
Sensory, <i>n</i> (%)	41/73 (56) <sup>°</sup>	15/29 (52) <sup>°°</sup>	2/8 (25)	58/110 (53) <sup>°°°</sup>	1/15 (7)	14.7	0.005
Sphincter, <i>n</i> (%)	1/73 (1.3)	1/29 (3.4)	0/8 (0)	2/110 (2)	0/15 (0)	0.98	0.91
Motor-sensory, <i>n</i> (%)	8/73 (11) <sup>^</sup>	3/29 (10) <sup>^^</sup>	5/8 (62)	16/110 (15) <sup>^^^</sup>	6/15 (40)	21.3	0.0003
Motor-sensory-sphincter, <i>n</i> (%)	5/73 (6)	2/29 (6)	1/8 (12)	8/110 (7)	4/15 (27)	1.06	0.90
Motor-sphincter, <i>n</i> (%)	3/73 (4)	0/29 (0)	0/8 (0)	3/110 (3)	1/15 (7)	2.2	0.70
Sensory-sphincter, <i>n</i> (%)	8/73 (11)	5/29 (17)	0/8 (0)	13/110 (12)	0/15 (0)	4.1	0.39

IATM, idiopathic acute transverse myelitis; DAATM, disease-associated acute transverse myelitis; PATM, possible acute transverse myelitis; NIATM, non-inflammatory acute transverse myelopathies; *n* = number of subjects. Chi-square test for large contingency tables was used

\**P* = 0.014, IATM vs NIATM; \*\**P* = 0.0036, ATM (all) vs NIATM (Fisher's exact test)

<sup>°</sup>*P* = 0.006, IATM vs NIATM; <sup>°°</sup>*P* = 0.0034, DAATM vs NIATM; <sup>°°°</sup>*P* = 0.0006, ATM (all) vs NIATM (Fisher's exact test)

<sup>^</sup>*P* = 0.012, IATM vs NIATM; <sup>^^</sup>*P* = 0.04, DAATM vs NIATM; <sup>^^^</sup>*P* = 0.026, ATM (all) vs NIATM (Fisher's exact test)

autoimmune myelitis (3 cases), and clinically isolated syndromes (3 cases). None of NIATM patients displayed serum AQP4 IgG (Table 3).

Three disease-associated but none of the idiopathic and possible ATM patients showed positive CSF virology consisting of positivity for HSV-1 and 2 DNA in two patients and VZV and CMV DNA in one patient. CSF analysis revealed a statistical trend towards a higher frequency of pleocytosis (> 10 cells/mm<sup>3</sup>) in disease-associated than in other ATM subgroups (chi-square = 9.4; *P* = 0.05). There was no significant difference among the ATM subgroups and NIATM with regard to frequency of high protein level as well as presence of CSF oligoclonal bands (Table 3).

### Electrophysiological findings of the ATM and NIATM patients

SSEPs were altered at a significantly higher frequency in idiopathic ATM than in other subgroups as well as compared to NIATM patients (chi-square = 10.7; *P* = 0.014). There was no significant difference in frequency of changes of VEPs neither of MEPs among ATM subgroups as well as NIATM patients (Table 3).

### MRI findings of the ATM and NIATM patients

Brain MRI showed T2-weighted lesions at a higher frequency in disease-associated than in idiopathic and possible ATM as well as NIATM patients (chi-square = 13.6; *P* = 0.0086). There were no significant differences among ATM subgroups in terms of GAD<sup>+</sup> lesions at spinal cord MRI. Conversely, ATM patients presented GAD<sup>+</sup> lesions at a significantly higher frequency compared with NIATM (chi-square = 24; *P* = < 0.0001). (Table 3).

### Clinical outcomes of the ATM and NIATM patients

The outcomes of the ATM subgroups as well as NIATM patients and the respective parameters are listed in Tables 4 and 5. There was no significant difference among ATM subgroups in terms of poor prognosis (Rankin score ≥ 3.0) at discharge. Conversely, NIATM patients showed a significantly higher frequency of poor prognosis than ATM patients (chi-square = 24; *P* < 0.0001) (Table 4). ATM patients with high disability at discharge were found to have a significantly higher age than those with lower disability (*P* = 0.0013). Conversely, there was no significant difference in terms of time to admission, number of GAD<sup>+</sup> MRI lesions as well as number of spinal cord segments involved, CSF protein levels as well as oligoclonal bands, and serum AQP4 IgG between ATM patients with good and poor prognosis. When considering the clinical symptoms at onset, occurrence of motor-sensory without (OR = 3.87; *P* = 0.04) and with sphincter dysfunction was significantly more frequent in patients with high disability than in those with low disability at discharge (OR = 7.4; *P* = 0.0009) (Table 5).

### Analysis of variables associated with poor prognosis of the ATM patients

Among the variables analyzed, higher age (*P* = 0.001) and motor-sensory without and with-sphincter involvement at onset (*P* = 0.002) were significantly associated with a high disability score at discharge (Table 6).

### Clinical follow-up of the cohorts

Clinical findings at follow-up were reported in Table 7. At a clinical follow-up with a median time of 1 year (range 0.5 to 4 years), only three relapses were recorded in ATM patients, one in the idiopathic and two in the disease-associated group.

**Table 3** Laboratory, electrophysiological, and MRI findings of the ATM and AM patients

	IATM (n = 73)	DAATM (n = 29)	PATM (n = 8)	ATM (all) (n = 110)	NIATM (n = 15)	Chi-square	P
<b>Laboratory</b>							
Serum AQP4- IgG, n (%)	0/52 (0)	8/19 (42)*	0/3 (0)	8/74 (11)	0/6 (0)	27.6	< 0.0001
CSF pleocytosis (> 10 cells/mm <sup>3</sup> ) n (%)	18/73 (25)	12/29 (41)	0/8 (0)	30/110 (27)	1/15 (7)	9.4	0.05
CSF high protein (> 0.5 g/l), n (%)	14/73 (19)	3/29 (10)	1/8 (12)	18/110 (17)	6/15 (40)	6.5	0.16
OB, n (%)	22/73 (30)	10/29 (35)	1/8 (12)	33/110 (30)	1/15 (7)	5.2	0.26
<b>Electrophysiology</b>							
VEP abnormal, n, (%)	4/21 (19)	9/23 (39)	2/7 (29)	15/51 (29)	0/1 (0)	2.6	0.46
SSEP abnormal, n (%)	38/50° (76)	5/12 (42)	5/6 (83)	48/68 (71)°°	2/7(29)	10.7	0.014
MEP abnormal, n (%)	13/20 (65)	4/6 (67)	2/3 (67)	19/29 (66)	3/8 (38)	2.0	0.56
<b>Brain MRI</b>							
T2 lesions, n (%)	25/49 (51)^	20/28 (71)^^	0/8 (0)	45/85 (53)^^^	3/8 (38)	13.6	0.0086
GAD+ lesions, n (%)	3/49 (6)	2/28 (7)	0/8 (0)	5/85 (6)	0/8 (0)	1.1	0.77
<b>SC MRI</b>							
T2 lesions, n (%)	72/73 (99)	28/29 (97)	7/8 (88)	107/110 (97)	15/15 (100)	4.3	0.23
GAD+ lesions, n (%)	49/73 (67)§	18/29 (62)§§	0/7 (0)	67/110 (61)§§§	2/15 (13)	24.0	< 0.0001

IATM, idiopathic acute transverse myelitis; DAATM, disease-associated acute transverse myelitis; PATM, possible acute transverse myelitis; NIATM non-inflammatory acute transverse myelopathies; CSF cerebrospinal fluid; n number of subjects; OB, oligoclonal bands; VEP, visual evoked potentials; SSEP, somatosensory evoked potentials; MEP, motor-evoked potentials; SC MRI, spinal cord MRI; GAD<sup>+</sup>, gadolinium-enhancing lesions. Chi-square test for large contingency tables was used

\*P = 0.0035, DAATM vs NIATM (Fisher’s exact test)

°P = 0.02, IATM vs NIATM, °°P = 0.037, ATM (all) vs NIATM (Fisher’s exact test)

^P = 0.007, IATM vs PATM, ^^P = 0.0004, DAATM vs PATM, ^^P = 0.0058, ATM (all) vs PATM (Fisher’s exact test)

§ P = 0.0003, IATM vs NIATM; §§ P = 0.003 DAATM vs NIATM, P = 0.0034, P = 0.0006 ATM (all) vs NIATM (Fisher’s exact test)

Four ATM patients had conversion to multiple sclerosis (MS), all belonging to the disease-associated group (3 with a clinically isolated syndrome at onset and 1 with ADEM). These patients were all female subjects, aged between 30 and 41, and displayed CSF oligoclonal bands at the myelitis onset. Out of 95 ATM patients with low disability at discharge (Rankin score < 3.0), 83 (87.4%) were clinically followed up and displayed absence of disability (Rankin score 0.0 or 1.0). Conversely, 7 of 12 (58%) ATM patients with high disability at discharge (Rankin score > 3.0) at follow-up showed high or moderate disability (Rankin score 3.0 or 2.0, respectively) and 5 had complete recovery (Rankin score 0.0).

Of the seven patients with poor (Rankin 3.0) or fair (Rankin 2.0) prognosis at the follow-up, six (86%) have had motor-sensory-sphincter and one motor-sphincter involvement at the disease onset. Of the three NIATM patients followed-up, one died and two had a fair prognosis.

**Discussion**

This study attempted to establish possible differences in terms of clinical, laboratory, and neuroradiological features among the ATM subgroups as defined by TMCWG criteria and with

**Table 4** Frequency of clinical disability at discharge of the ATM and NIATM patients

	IATM (n = 73)	DAATM (n = 29)	PATM (n = 8)	ATM (all) (n = 110)	NIATM (n = 15)	Chi-square	P
Rankin < 3.0, n (%)	63 (86)*	26 (90)**	6 (75)	95 (86)*	5 (33)	24.0	< 0.0001
Rankin ≥ 3.0, n (%)	10 (14)*	3 (10)**	2 (25)	15 (14)*	10 (67)	24.0	< 0.0001

IATM, idiopathic acute transverse myelitis; DAATM, disease-associated acute transverse myelitis; PATM, possible acute transverse myelitis; NIATM, non-inflammatory acute transverse myelopathies;; n = number of subjects. Chi-square test for large contingency tables was used

\*P < 0.0001, IATM and ATM (all) vs. NIATM (Fisher’s exact test)

\*\*P = 0.0002, DAATM vs NIATM (Fisher’s exact test),

**Table 5** Clinical, laboratory, MRI features, and outcomes at discharge of the ATM patients

	Rankin $\geq$ 3.0 ( <i>n</i> = 15)	Rankin < 3.0 ( <i>n</i> = 95)	OR (95% CI)	<i>P</i>
Age (years) (mean $\pm$ SEM)	59 $\pm$ 4.9	44 $\pm$ 1.6	n.a.	0.0013
Time to admission (days) (mean $\pm$ SEM)	3.3 $\pm$ 1.0	7.7 $\pm$ 1.0	n.a.	0.10
CSF proteins (g/L) (mean $\pm$ SEM)	0.49 $\pm$ 12	0.38 $\pm$ 4	n.a.	0.28
CSF OB, <i>n</i> (%)	7/15 (47)	26/95 (27)	2.3 (0.8–6.8)	0.14
SC MRI GAD <sup>+</sup> , <i>n</i> (%)	8/15 (67)	56/95 (59)	0.79 (0.25–2.2)	0.78
SC MRI segments, number (mean $\pm$ SEM)	2.9 $\pm$ 0.5	2.3 $\pm$ 0.3	n.a.	0.45
Motor-sensory, <i>n</i> (%)	5/15 (33)	11/95 (12)	3.8 (1.2–11.9)	0.04
Motor-sensory-sphincter, <i>n</i> (%)	4/15 (27)	5/95 (5)	6.5 (1.74–27.5)	0.019
Motor sensory/motor-sensory-sphincter, <i>n</i> (%)	9/15 (60)	16/95 (17)	7.4 (2.2–25.5)	0.0009

*n*, number of subjects; *CSF*, cerebrospinal fluid; *OB*, oligoclonal bands; *SC MRI GAD*<sup>+</sup>, spinal cord MRI gadolinium-enhancing lesions; *n.a.*, not applicable; *OR*, odds ratio; *95% CI*, 95% confidence interval. Unpaired T test for comparison of means and Fisher's exact test for comparison of frequencies were used, respectively. OR values were calculated to assess the risk

respect to NIATM patients as well as to identify possible prognostic factors. All studies carried out prior to the established TMCGW criteria were mainly based on small single-center cohorts often including non-inflammatory AM and underpowered to allow to reach statistical significance [3–5]. Although the TMCGW criteria are questionable as they do not include cases with partial ATM [17], however, they represent an advance in the understanding of this heterogeneous disorder often without any identifiable cause and thus characterized as idiopathic. The estimation of the incidence of idiopathic ATM reported in different studies is almost various ranging from 9 to 60% of the cases [18–21]. In our multicenter cohort, 66% of the patients were classified as idiopathic ATM. A long-term follow-up was found to reduce the number of patients with idiopathic ATM [22], and this could partly explain the variability of

frequency found in different studies. In our study, the only clinical characteristic able to distinguish idiopathic and disease-associated ATM from NIATM patients was a significantly lower age associated with a lower disability at the admission. This is consistent with the finding of a higher age of patients with spinal cord infarcts compared with ATM patients [5, 19]. The neurological symptomatology at the onset was previously analyzed in a few studies [19]. In our study, we found that ATM group irrespective of distinction between idiopathic and disease-associated patients may be distinguishable from NIATM patients as presenting more sensory and less motor symptoms at onset. To our knowledge, this finding was not previously reported.

In addition, CSF findings did not allow to differentiate the ATM subgroups. We detected serum AQP4 IgG exclusively in the disease-associated ATM subgroup comprising patients

**Table 6** Analysis of the variables associated with poor prognosis in ATM patients

Univariate analysis			
Variable	<i>P</i>	Score	
Age	0.000	12.74	
Time to admission	0.088	2.91	
Motor-sensory involvement	0.11	2.54	
Motor-sensory-sphincter involvement	0.03	4.67	
Motor-sensory/motor-sensory-sphincter involvement	0.001	10.9	
Sensory pain involvement	0.372	0.79	
Spinal cord segments	0.66	0.194	
Oligoclonal bands	0.14	2.17	
Multivariate analysis			
Variable	<i>P</i>	OR	95% CI
Age	0.001	1.08	1.031–1.132
Motor-sensory/motor-sensory-sphincter involvement	0.002	9.52	2.27–39.8

*OR*, odds ratio; *95% CI*, 95% confidence interval. Stepwise logistic regression for univariate and multivariate analysis was used

**Table 7** Clinical features and outcomes at follow-up (the median of follow-up time was 1 year (IQR = 0.5–4))

Rankin score	0/1.0	2.0	3.0	Death
ATM ( <i>n</i> = 95)	89 (94%)	2 (2%)	4 (4%)	0
NIATM ( <i>n</i> = 3)	0	2 (67%)	0	1 (33%)
Myelitis relapse				
ATM ( <i>n</i> )	3/95 (3%)			
Conversion to MS				
ATM ( <i>n</i> )	4/95 (4%)			

ATM, acute transverse myelitis; NIATM, non-inflammatory acute transverse myelopathy; *n* = number of subjects

with NMO or MS confirming this antibody be a specific biomarker of NMOSD thought able to predict possible occurrence of relapsing myelitis [23], although it was rarely found in partial ATM [24]. Positive virology for neurotropic virus DNA was rarely detected in our cohort and however, only in disease-associated ATM patients as previously found [19].

Electrophysiological findings were not different both in ATM subgroups and NIATM consisting with other studies [14, 20] except for a higher frequency of altered SSEPs in all ATM group compared with NIATM paralleling the finding of a higher frequency of sensory symptoms at onset in ATM than in NIATM patients.

With regard to neuroradiological assessment, the frequency of spinal cord GAD<sup>+</sup> lesions did not allow to differentiate any ATM subgroup but was higher in all ATM than that in NIATM patients. Enhancing and swelling lesions were previously found in spinal cord of ATM patients [25].

Of interest are the findings on clinical outcomes. Prognosis in ATM is variable and the frequency of poor outcome is different in several studies [3, 4]. Our study found that only 14% of ATM patients presented elevated disability at discharge, and of these, almost a half continued to have high disability after a median 1-year-follow-up. Conversely, 66% of NIATM patients had poor prognosis at discharge, and of these, 40% died or continued to have high disability at the follow-up. Previous studies showed a poor prognosis in 35 to 40% of idiopathic ATM patients [9, 26]. This difference may be due to the selection of patients fulfilling the TMSGW criteria with different response to treatments and with a natural benign course. Incidence of relapsing myelitis was low in our cohort and was found in one idiopathic ATM only. Relapsing TM may occur as conversion to MS but may also be a distinct disorder from MS [27–29]. These findings seem to confirm that ATM is mainly a benign disorder although it could be severe in a subgroup of patients experiencing great functional impairment over time. A number of clinical prognostic factors were studied in ATM and NIATM patients including age, time to admission, severity of onset

symptoms at onset, sphincter dysfunction, back pain, and also laboratory markers such as CSF cystatin [7], anti-myelin oligodendrocyte glycoprotein antibodies (MOG) [8], and 14-3-3 [30, 31] with different and conflicting findings. A recent single-center study on 87 idiopathic ATM patients found sphincter involvement and long extensive transverse myelitis on MRI as the most significant poor prognostic factors [26]. The discrepancy in searching for prognostic factors may in part be due to differences in clinical diagnostic criteria as well as in prognosis assessment often based on qualitative clinical parameters only but not on quantitative disability scores. In our study, using the Rankin scale to assess disability, we identified two variables associated with a poor prognosis: higher age and a complex symptomatology at onset consisting of association of motor-sensory symptoms with sphincter impairment. The presence of both variables increased significantly the risk of a poor prognosis both at short and at longer time. The majority of the previous studies assessed prognosis after a various clinical follow-up. We analyzed the disability at discharge as a short-term prognostic indicator revealing that a poor prognosis at discharge tends to remain stable or to little change over time, whereas, conversely, a favorable prognosis at discharge may rarely be lost at follow-up. The identification of significant variables influencing short-term prognosis of ATM could help to better manage treatment preventing possible clinical complications thought to frequently occur during hospitalization. One limitation of our study, like others, is the retrospective design that is partially mitigated by the multicenter nature. Otherwise, the low incidence of ATM estimated over different countries in the world [4, 5, 32], makes very difficult to design prospective investigations. Another limitation factor is the small size of the NIATM group suggesting more caution in the conclusions. In our study, we did not take into account the role of treatments that, however, were almost homogeneous for all ATM patients mainly consisting of high-dose IV corticosteroids and thus unlikely to significantly influence the prognosis.

In conclusion, this study suggests some issues. Our findings do not allow to identify any clinical or laboratory characteristics suitable for differentiating the ATM subgroups. However, when a sensory but not motor symptomatology occurs at the onset, a diagnosis of ATM may prevail with respect to that of NIATM. In addition, when ATM diagnosis has been achieved, a patient older and with a complex symptomatology at the admission consisting of simultaneous occurrence of motor-sensory disturbances with or without sphincter impairment could experience a major risk of a poor prognosis both at the discharge and at the follow-up thus requiring a more adequate and timely treatment.

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## Compliance with ethical standards

All study documents and procedures were approved by the Ethic Committee of the Medical School of the University of Siena and the local ethics boards of the other participating centers. All patients gave their informed consent.

**Conflict of interest** G.M., C.C., M.G., E.M., and F.V. declare no financial or other conflicts of interest. P.A. received financial support from Novartis, Biogen, and Almirall for research and attending meetings. G.L.M. received financial support from Biogen Idec, Merck Serono, Novartis, Teva, Genzyme, and Sanofi Aventis for lecturing, travel expenses, attending meetings, and research. A.L. received financial support for travel and attending meeting from Merck, Sanofi Genzyme, Teva, Biogen and Novartis. E.D'A. reports personal fees from Teva, Merck Serono, Biogen, Bayer, and Novartis. F.P. received personal compensation for advisory board and speaking activities from Almirall, Biogen, Cilgane, Merck, Novartis, Roche, Sanofi, and Teva. P.S. has received speaker and advisory boards honoraria and travel grants from TEVA, Merck Serono, Sanofi-Genzyme, Novartis, and Biogen.

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