REVISED MCDONALD 2010 VERSUS MAGNIMS 2016 MRI CRITERIA IN CIS PATIENTS SUGGESTIVE OF MS: A MULTICENTRE STUDY

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INTRODUCTION and PURPOSE

In 2001 MRI was formally included in the diagnostic criteria for multiple sclerosis (MS) to provide objective evidence for disease dissemination in space (DIS) and time (DIT) and to exclude alternative diagnoses [1]. Since their introduction, these criteria have been modified to simplify them, to clarify specific aspects and to enable earlier diagnosis of MS [2-4]. Since their last revision (the revised McDonald 2010 criteria) [3], new evidences regarding the application of MRI for MS diagnosis become available. Modifications of MRI diagnostic criteria have been proposed in 2016 with the definition of the "MAGNIMS 2016" criteria [5], which include: 1) the removal of any distinction between symptomatic and asymptomatic lesions; 2) increasing from 1 to 3 lesions to define periventricular (PV) involvement; 3) combining "cortical/juxtacortical" lesions to expand the concept of juxtacortical (JC) involvement; and 4) adding the optic nerve (ON) as an additional lesion location.

The aim of this study was to compare the performance of the MAGNIMS 2016 criteria [5] and the revised McDonald 2010 criteria [3] for the development of clinically definite (CD) MS in a large multicente cohort of patients with a clinically isolated syndrome (CIS) suggestive of MS, collected within the MAGNIMS network. In the same cohort, the influence of each individual modification from the MAGNIMS criteria [5] was also assessed to investigate its potential contribution to future modifications of MS diagnostic criteria.

METHODS

- **Patients**. This project was run within the European MAGNIMS network (http://www.magnims.eu) and involved eight centres (Milan and Rome [Italy], Amsterdam [the Netherlands], Barcelona [Spain], Belgrade [Serbia], Copenhagen [Denmark], Graz [Austria], London [UK]).
- **Inclusion/exclusion criteria**. CIS patients recruited into prospective MRI and clinical follow-up (FU) studies with the following criteria: (a) age ≥16 and ≤60 years; (b) a first CIS suggestive of CNS demyelination [6]; (c) a typical clinical presentation of relapsing-remitting MS [7]; (d) a complete neurological examination; (e) a baseline brain and spinal cord (SC) MRI scan obtained ≤3 months from the clinical onset; (f) a FU brain scan obtained ≤12 months from CIS onset; and (g) careful exclusion of alternative diagnoses, comorbidities (psychiatric or other neurological disorders) and/or previous clinical events suggestive of demyelination.
- **Study flow chart**. **Figure 1**.

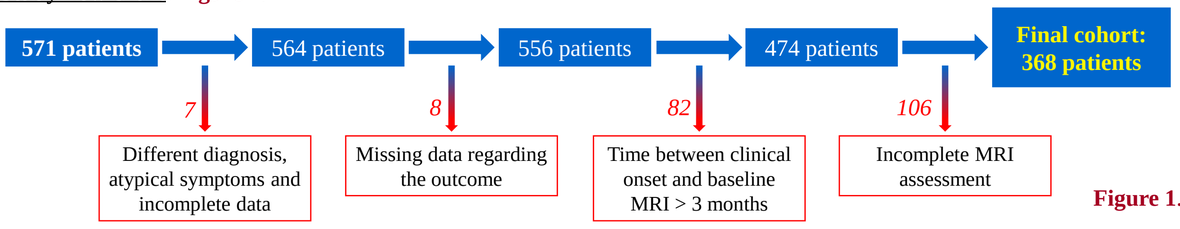


Figure 1.

- **MRI and visual evoked potentials (VEP)**. Brain and spinal cord MRI scans had been obtained at 1.0 Tesla (4.1%), 1.5 Tesla (66.0%) or 3.0 Tesla (29.9%).
- Brain MRI scans (baseline and FU). Axial DE and/or FLAIR and post-contrast T1-weighted sequences. A double inversion recovery (DIR) sequence was available for 167/368 (45.4%) CIS patients from three centres (Barcelona, Belgrade and Milan).
- Spinal cord MRI scans (baseline). Sagittal short tau inversion recovery (STIR) and/or T2-weighted and post-contrast T1-weighted sequences, covering the cervical and thoracic cord.
- ON involvement. Assessment of ON involvement was performed in 241 (65.5%) CIS patients and it was based on VEP in 219/241 (90.9%) patients, ON MRI in 3/241 (1.2%) patients and both VEP and ON MRI in 19/241 (7.9%) patients.
- **MRI analysis**. The following items were evaluated: total number of white matter (WM) lesions, number of PV, JC, posterior fossa (PF) and SC lesions. The combination of cortical (CL) and JC lesions was quantified by combining lesion counts obtained from DIR (when available) and T2/FLAIR sequences. Gadolinium (Gd)-enhancing lesions were identified on post-contrast T1-weighted scans. To evaluate the effects of symptomatic lesions, if a subject had a brainstem or SC syndrome, we counted lesions both including and excluding those lesions present in the symptomatic regions. From the FU MRI scans, the numbers of new T2-hyperintense and Gd-enhancing lesions were quantified.
- **DIS and DIT criteria**. On baseline MRI scans, the following DIS criteria were assessed (**Table 1**): 1) revised McDonald 2010 criteria [3]; 2) MAGNIMS 2016 criteria [5]; 3) modified DIS criteria 1 (symptomatic): revised McDonald 2010 criteria modified to include lesions in symptomatic regions (brainstem and SC) in the lesion count; 4) modified DIS criteria 2 (3PV): revised McDonald 2010 criteria modified to change to 3 the minimum number of lesions necessary to define PV involvement; 5) modified DIS criteria 3 (CL/JC): revised McDonald 2010 criteria modified to combine CL and JC; 6) modified DIS criteria 4 (ON): revised McDonald 2010 criteria modified to include ON involvement as an additional location for the definition of DIS (defined by the presence of a lesion on MRI and/or VEP abnormalities).
  On baseline and FU MRI, DIT was defined according to the 1) revised McDonald 2010 criteria [3] and 2) MAGNIMS 2016 criteria [5].
  The fulfilment of DIS plus DIT criteria for all DIS criteria was also assessed.

Table 1.

DIS criteria					
Revised McDonald 2010 [3]	≥ 2 of the following:				
	≥ 1 PV lesion	≥ 1 JC lesion		≥ 1 PF lesion	≥ 1 SC lesion
	All lesions in symptomatic regions excluded in brainstem and SC syndromes				
MAGNIMS 2016 [5]	≥ 2 of the following:				
	≥ 3 PV lesions	≥ 1 CL/JC lesion	≥ 1 PF lesion	≥ 1 SC lesion	≥ 1 ON lesion
	All lesions in symptomatic regions included in brainstem and SC syndromes				
DIT criteria					
Revised McDonald 2010 [3]	Simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions at any time or A new T2 and/or Gd-enhancing lesion on FU MRI irrespective of timing of baseline scan				
MAGNIMS 2016 [5]	Simultaneous presence of Gd-enhancing and non-enhancing lesions at any time (including symptomatic lesions) or A new T2 and/or Gd-enhancing lesion on FU MRI irrespective of timing of baseline scan				

- **Statistical analysis**.
- Outcome. Development of CDMS (occurrence of a second clinical event). Time to CDMS was calculated as the interval between the onset of the first and second events.
- Performance of the MRI criteria for DIS, DIT and DIS plus DIT. Cumulative/dynamic time-dependent ROC curve analysis [8] for censored survival data using the clinical status (CDMS or CIS) over time as the outcome. Sensitivity, specificity, accuracy, positive and negative predictive values at months 36 (M36) and 60 (M60) were calculated. Bias-corrected and accelerated bootstrap method [9] was used to estimate 95% CIs.
- Cumulative risk of CDMS development up to the last available FU. Kaplan-Meier survival curves (patients censored according to their FU).
- Adjusted hazard ratios (aHRs) to CDMS conversion. Extended Cox regression models using time to CDMS as the outcome and adjusted for age, sex, treatment (time-dependent), disease onset type (optic neuritis *vs* others), and presence of oligoclonal bands. A gamma-frailty term was also included to address centre effects [10].

RESULTS

Table 2 summarizes the main baseline demographic, clinical and MRI findings of the CIS patients included.

	All cases (n=368)
Demographic details	
Number (%) of	
•Men	126 (34.2%)
•Women	242 (65.8%)
Median age at onset (range) [years]	32.5 (16-59)
Clinical details	
Median DD at baseline MRI (range) [months]	1.8 (0.0-3.0)
Median EDSS at baseline (range)	1.5 (0.0-5.0)
Clinical presenting symptom(s) (%):	
Monofocal	340 (92.4%)
•Optic neuritis	•169/340 (49.7%)
•Brainstem/cerebellar syndrome	•61/340 (18.0%)
•Spinal cord syndrome	•79/340 (23.2%)
•Hemispheric syndrome	•31/340 (9.1%)
Multifocal	28 (7.6%)
Number (%) of patients with CSF analysis	256 (69.6%)
Number (%) of patients with oligoclonal bands	176/256 (68.8%)
Number (%) of patients receiving treatment at FU	157 (42.7%)
CDMS at 12 months from onset (%)	99 (26.9%)
CDMS at FU (%)	189 (51.4%)
Median time to CDMS (range) [months]	10.9 (1.0-178.6)
Median FU duration in not converters (range) [months]	36.2 (1.6-228.3)

MRI details		
Median time to baseline MRI (range) [months]		1.8 (0.0-3.0)
Baseline number (%) of patients with lesions (brain and cord)		333 (90.5%)
Median lesion number (range)		11 (0-248)
Median time to FU MRI (range) [months]		6.4 (3.0-12.0)
MRI criteria		
Baseline number (%) of patients with	**≥ 1 PV lesion**	292 (79.3%)
	≥ 3 PV lesions	231 (62.8%)
	≥ 1 JC lesion	259 (70.4%)
	≥ 1 CL/JC	266 (72.3%)
	≥ 1 PF lesion	165 (44.8%)
	≥ 1 SC lesion	173 (47.0%)
	symptomatic lesions*	128 (34.8%)
	≥ 1 Gd-enhancing lesion	150 (40.8%)
Number (%) of patients with ≥ 1 new T2/Gd-enhancing lesion at FU MRI		184 (50.0%)

*for patients with a brainstem or spinal cord syndrome.

Table 2.

Performance of the MRI criteria for DIS, DIT and DIS plus DIT.

Table 3 shows the performance of revised McDonald 2010 [3] and MAGNIMS 2016 [5] criteria.

Criteria	Timepoint	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS only						
Revised McDonald 2010 [3]	**M36**	0.91 (0.85-0.94)	0.33 (0.25-0.42)	0.62 (0.57-0.67)	0.56 (0.49-0.62)	0.79 (0.67-0.87)
	M60	0.87 (0.80-0.91)	0.33 (0.21-0.46)	0.60 (0.53-0.67)	0.65 (0.57-0.72)	0.63 (0.47-0.76)
MAGNIMS 2016 [5]	**M36**	0.93 (0.88-0.96)	0.32 (0.24-0.41)	0.63 (0.58-0.67)	0.56 (0.50-0.63)	0.83 (0.71-0.91)
	M60	0.90 (0.83-0.94)	0.34 (0.23-0.48)	0.62 (0.56-0.69)	0.66 (0.59-0.73)	0.70 (0.54-0.82)
DIT alone						
Revised McDonald 2010 [3]	**M36**	0.78 (0.71-0.84)	0.44 (0.35-0.53)	0.61 (0.55-0.67)	0.58 (0.51-0.65)	0.67 (0.57-0.76)
	M60	0.78 (0.71-0.84)	0.49 (0.37-0.62)	0.63 (0.56-0.71)	0.69 (0.61-0.77)	0.60 (0.48-0.70)
MAGNIMS 2016 [5]	**M36**	0.80 (0.73-0.85)	0.42 (0.33-0.50)	0.61 (0.55-0.66)	0.57 (0.50-0.64)	0.68 (0.57-0.77)
	M60	0.79 (0.72-0.85)	0.46 (0.33-0.59)	0.62 (0.55-0.69)	0.68 (0.60-0.76)	0.59 (0.46-0.70)
DIS plus DIT						
Revised McDonald 2010 [3]	**M36**	0.73 (0.66-0.80)	0.50 (0.42-0.59)	0.62 (0.56-0.67)	0.58 (0.51-0.65)	0.67 (0.58-0.75)
	M60	0.72 (0.64-0.78)	0.52 (0.39-0.65)	0.62 (0.54-0.69)	0.68 (0.59-0.76)	0.56 (0.45-0.67)
MAGNIMS 2016 [5]	**M36**	0.77 (0.70-0.83)	0.50 (0.41-0.59)	0.64 (0.58-0.69)	0.60 (0.52-0.67)	0.70 (0.61-0.78)
	M60	0.76 (0.68-0.82)	0.52 (0.39-0.65)	0.64 (0.57-0.71)	0.69 (0.61-0.77)	0.60 (0.49-0.70)

Table 3.

Figure 2 shows the area under the curve (AUC) over time, up to 10 years, from disease onset of the revised McDonald 2010 [3] and MAGNIMS 2016 [5] criteria according to the development of CDMS.

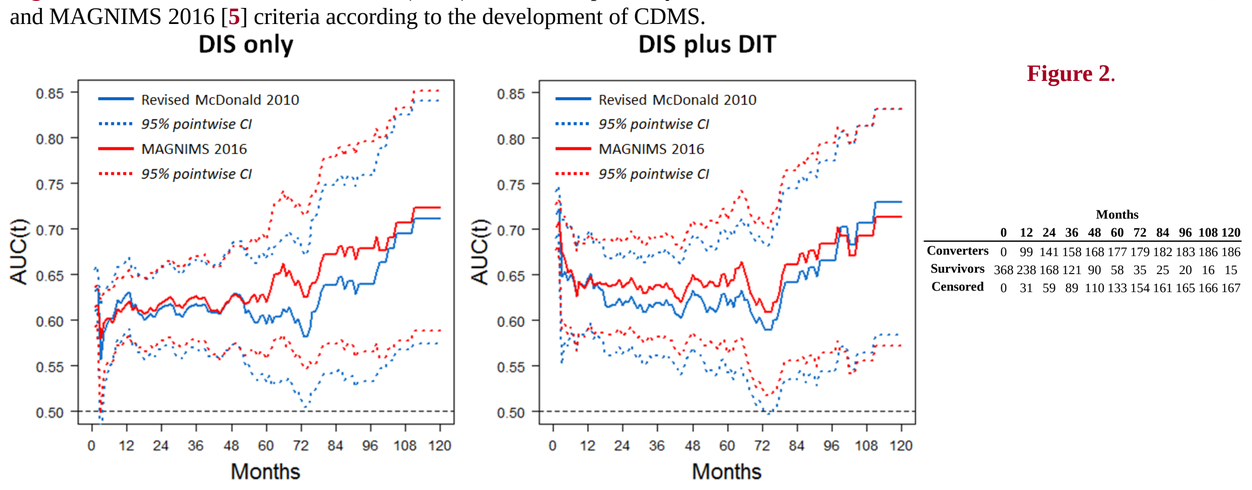


Figure 2.

Table 4 shows the performance of the different modified MRI criteria.

Criteria	Timepoint	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS only						
Modified DIS criteria 1 (symptomatic)	**M36**	0.92 (0.87-0.96)	0.31 (0.23-0.40)	0.62 (0.57-0.66)	0.56 (0.49-0.62)	0.80 (0.69-0.89)
	M60	0.88 (0.81-0.92)	0.33 (0.22-0.46)	0.60 (0.54-0.67)	0.65 (0.58-0.72)	0.65 (0.49-0.79)
Modified DIS criteria 2 (3PV)	**M36**	0.85 (0.78-0.90)	0.40 (0.32-0.50)	0.63 (0.57-0.68)	0.57 (0.51-0.64)	0.74 (0.63-0.82)
	M60	0.82 (0.75-0.87)	0.41 (0.29-0.55)	0.62 (0.55-0.69)	0.66 (0.59-0.74)	0.61 (0.48-0.73)
Modified DIS criteria 3 (CL/JC)	**M36**	0.92 (0.87-0.95)	0.32 (0.24-0.41)	0.62 (0.57-0.67)	0.56 (0.50-0.62)	0.81 (0.69-0.89)
	M60	0.88 (0.81-0.92)	0.31 (0.20-0.44)	0.59 (0.53-0.66)	0.64 (0.57-0.71)	0.64 (0.47-0.77)
Modified DIS criteria 4 (ON)	**M36**	0.92 (0.87-0.96)	0.26 (0.18-0.34)	0.59 (0.55-0.64)	0.54 (0.48-0.60)	0.78 (0.64-0.88)
	M60	0.90 (0.84-0.94)	0.26 (0.16-0.38)	0.58 (0.52-0.65)	0.63 (0.56-0.70)	0.64 (0.46-0.79)
DIS plus DIT						
Modified DIS criteria 1 (symptomatic)	**M36**	0.76 (0.69-0.83)	0.49 (0.40-0.58)	0.62 (0.57-0.68)	0.58 (0.51-0.65)	0.68 (0.60-0.77)
	M60	0.74 (0.66-0.80)	0.50 (0.36-0.62)	0.62 (0.55-0.69)	0.68 (0.59-0.75)	0.57 (0.46-0.68)
Modified DIS criteria 2 (3PV)	**M36**	0.70 (0.63-0.77)	0.55 (0.46-0.63)	0.62 (0.56-0.68)	0.59 (0.51-0.67)	0.66 (0.57-0.74)
	M60	0.69 (0.61-0.76)	0.55 (0.42-0.68)	0.62 (0.54-0.69)	0.69 (0.60-0.77)	0.56 (0.45-0.66)
Modified DIS criteria 3 (CL/JC)	**M36**	0.75 (0.67-0.81)	0.50 (0.42-0.60)	0.63 (0.57-0.68)	0.59 (0.51-0.66)	0.68 (0.59-0.76)
	M60	0.73 (0.65-0.79)	0.52 (0.39-0.64)	0.62 (0.55-0.69)	0.68 (0.59-0.76)	0.57 (0.45-0.67)
Modified DIS criteria 4 (ON)	**M36**	0.75 (0.67-0.81)	0.48 (0.39-0.57)	0.61 (0.56-0.67)	0.57 (0.50-0.65)	0.67 (0.57-0.75)
	M60	0.74 (0.66-0.80)	0.50 (0.36-0.62)	0.62 (0.54-0.69)	0.68 (0.60-0.75)	0.57 (0.46-0.68)

Table 4.

aHRs using CDMS as the outcome. **Table 5** shows the aHRs and their corresponding 95% CIs obtained from extended Cox regression models using CDMS as the outcome.

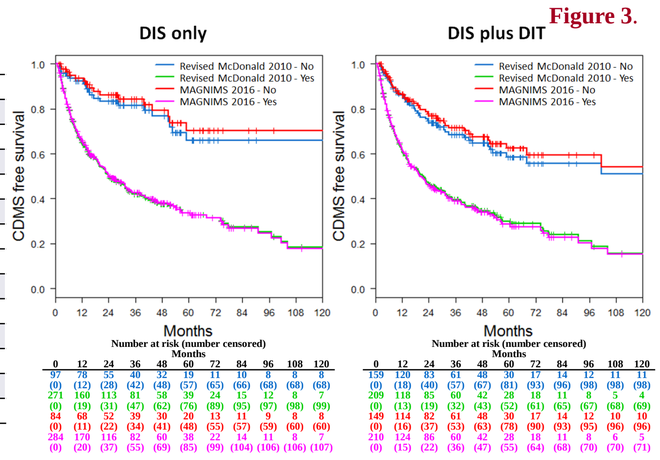
Cumulative risk of CDMS development up to the last available FU. **Figure 3** shows Kaplan-Meier curves representing the survival probability estimates of not developing CDMS up to 10 years from disease onset considering DIS only or DIS plus DIT according to the revised McDonald 2010 [3] and MAGNIMS 2016 [5] criteria

Table 5.

Criteria	aHR* (95% CI)	p value
DIS only		
Revised McDonald 2010 [3]	3.48 (2.16-5.62)	<0.0001
MAGNIMS 2016 [5]	4.43 (2.59-7.56)	<0.0001
Modified DIS criteria 1 (symptomatic)	3.59 (2.18-5.93)	<0.0001
Modified DIS criteria 2 (3PV)	3.13 (2.06-4.76)	<0.0001
Modified DIS criteria 3 (CL/JC)	3.66 (2.24-6.00)	<0.0001
Modified DIS criteria 4 (ON)	3.34 (1.98-5.64)	<0.0001
DIS plus DIT		
Revised McDonald 2010 [3]	2.52 (1.78-3.58)	<0.0001
MAGNIMS 2016 [5]	2.95 (2.04-4.26)	<0.0001
Modified DIS criteria 1 (symptomatic)	2.54 (1.77-3.65)	<0.0001
Modified DIS criteria 2 (3PV)	2.54 (1.80-3.58)	<0.0001
Modified DIS criteria 3 (CL/JC)	2.60 (1.83-3.71)	<0.0001
Modified DIS criteria 4 (ON)	2.58 (1.81-3.67)	<0.0001

*=adjusted for age, sex, centre, treatment, type of onset and oligoclonal bands.

Figure 3.



CONCLUSIONS

- **By evaluating a large multicentre cohort of patients experiencing a typical CIS, we found that the MAGNIMS 2016 criteria are easy to implement and they perform similarly to the revised McDonald 2010 criteria considering CDMS conversion at M36 and M60, with both criteria showing high sensitivity and accuracy and similar specificity.**
- **Survival probability analyses confirmed that the two sets of criteria had similar performance, even though, compared to the revised McDonald 2010, the MAGNIMS 2016 DIS criteria had a higher aHR, which may be explained by the higher conversion-free survival in CIS patients not fulfilling the MAGNIMS 2016 criteria.**
- **The inclusion of lesions in the symptomatic region in CIS patients with a brainstem or SC onset did not affect performance of DIS and DIT diagnostic criteria, supporting the removal of this distinction, with a simplification of MRI criteria for DIS and DIT.**
- **The use of 3 lesions to define PV involvement reduced sensitivity (0.85 *vs* 0.91 at M36), but increased specificity (0.40 *vs* 0.33 at M36), without affecting diagnostic accuracy, suggesting that this criterion could improve the specificity of the MRI diagnostic criteria, reducing misdiagnosis and also representing a possible prognostic factor.**
- **The inclusion of CLs evaluation in the subgroup of CIS patients (45.4%) with DIR acquisition did not significantly influence DIS criteria performance, and only four additional patients fulfilled the DIS criteria. Our study confirmed MAGNIMS guidelines to use the combined term CL/JC to expand the concept of JC involvement.**
- **The inclusion of ON assessment in the definition of DIS in those patients who had VEP or optic nerve MRI evaluations slightly decreases specificity (0.26 *vs* 0.33 at M36), which is expected whenever additional criteria are included. Further studies aimed at validating MRI and neurophysiological measures of ON involvement as an additional DIS criterion should be undertaken.**

REFERENCES

1) McDonald et al., Ann Neurol 2001
2) Polman et al., Ann Neurol 2005
3) Polman et al., Ann Neurol 2011
4) Montalban et al., Neurology 2010
5) Filippi et al., Lancet Neurol 2016
6) Miller et al., Lancet Neurol 2005
7) Brownlee et al., Lancet 2017
8) Hung et al., Canadian Journal of Statistics 2010
9) Efron, Journal of the American Statistical Association 1987
10) Glidden et al., Stat Med 2004