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Diagnostic performance of central vein sign versus oligoclonal bands for multiple sclerosis

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Abstract

Background: Cerebrospinal fluid (CSF) oligoclonal bands (OCB) are a diagnostic biomarker in multiple sclerosis (MS). The central vein sign (CVS) is an imaging biomarker for MS that may improve diagnostic accuracy.

Objectives: To examine the diagnostic performance of simplified CVS methods in comparison to OCB in participants with clinical or radiological suspicion for MS.

Methods: Participants from the CentrAl Vein Sign in MS (CAVS-MS) pilot study with CSF testing were included. Select-3 and Select-6 (counting up to 3 or 6 CVS+ lesions per scan) were rated on post-gadolinium FLAIR* images. Sensitivity, specificity, positive (PPV) and negative predictive values for Select-3, Select-6, OCB, and combinations thereof were calculated for MS diagnosis at baseline and at 12 months.

Results: Of 53 participants, 25 were OCB+. At baseline, sensitivity for MS diagnosis was 0.75 for OCB, 0.83 for Select-3, and 0.71 for Select-6. Specificity for MS diagnosis was 0.76 for OCB, 0.48 for Select-3, and 0.86 for Select-6. At 12-months, PPV for MS diagnosis was 0.95 for Select-6 and 1.00 for Select-6 with OCB+ status.

Discussion: Results suggest similar diagnostic performance of simplified CVS methods and OCB. Ongoing studies will refine whether CVS could be used in replacement or in conjunction with OCB.

Keywords

biomarker; central vein sign; diagnostic imaging; multiple sclerosis; oligoclonal bands

Introduction

Establishing a diagnosis of multiple sclerosis (MS) is not always straightforward and can be especially challenging in cases with atypical clinical and radiological manifestations.[1] Studies show a high rate of misdiagnosis, with approximately 1 in 5 patients referred to an MS center with a prior diagnosis of MS not actually having the disease.[2–4] Misdiagnosis

occurs, among other factors, due to inappropriate application of the MS diagnostic criteria.[5] Incorrect application of magnetic resonance imaging (MRI) criteria with misclassification of dissemination in space (DIS) with lesions that are not characteristic of MS is considered to be a major cause of misdiagnosis.[5,6] Many of those misdiagnosed with MS (50–70%) are prescribed disease modifying therapies, which can confer unnecessary risks or harm.[3,4,7] Outside the physical and psychological impact of MS misdiagnosis, there are also associated economic costs.[8] Timely and accurate diagnosis and treatment of MS is crucial to minimize harm related to misdiagnosis and also to ensure early, appropriate identification and treatment of MS to prevent disease-related disability.

The central vein sign (CVS) is a novel imaging biomarker proposed as a tool to improve and simplify the diagnosis of MS. The CVS can differentiate MS lesions from mimics such as nonspecific white matter changes and microvascular injury.[9] Combining 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) and T2*-weighted images creates a single contrast (FLAIR*) in which the CVS can be easily identified as a central hypointensity within a hyperintense lesion.[10,11] The North American Imaging in MS Cooperative (NAIMS) published criteria for identification of the CVS.[11] Simplified CVS algorithms based on FLAIR* and counting up to 3 (Select-3) or 6 lesions (Select-6) performed well diagnosticly.[12,13]

The presence of cerebrospinal fluid (CSF) oligoclonal bands (OCB) unmatched in the serum is a well-established laboratory biomarker in MS and can be used as an alternative to supporting dissemination in time (DIT) per the 2017 McDonald Criteria.[14] OCB are also one of the criteria required to establish primary progressive MS.[14] To determine OCB status, CSF sampling through lumbar puncture is needed. Lumbar puncture is an invasive test and may be intolerable or anatomically challenging for some patients, may be associated with procedural risks, and accrues additional healthcare costs.[15,16] Kappa free light chains, in contrast to OCB assessment, may be less time consuming and is not rater-dependent. A prior study of clinically isolated syndrome (CIS) participants and non-MS controls showed that CVS had higher specificity than OCB for diagnosis of MS.[17] A dedicated comparison study assessing OCB and CVS as standalone or combination methods for diagnosis of MS has not been published. We sought to address this gap in the literature by leveraging the CentrAl Vein Sign in Multiple Sclerosis (CAVS-MS) pilot study.[18]

Methods

Study design

The CAVS-MS pilot study was an international multicenter observational study conducted by NAIMS with the goal of assessing the feasibility of multicenter CVS acquisition using a high resolution isotropic T2*-weighted segmented echo-planar imaging (EPI) in participants presenting with a clinical or radiological suspicion of MS.[18,19] For this study, participants with CSF data were selected to compare the diagnostic performance of CVS and OCB.

Participants

Adults, aged 18–65, who were enrolled in CAVS-MS and also had CSF analysis conducted as part of clinical workup were studied.[18,19] Main inclusion criteria were: age 18–65 (inclusive), referral to the academic site for a new clinical/radiological suspicion of MS, brain MRI scan demonstrating focal white matter T2-hyperintensities, and no prior exposure to disease modifying therapies. Main exclusion criteria were contraindications to or inability to tolerate to MRI, contraindications to use of gadolinium-based contrast agents, and treatment with systemic corticosteroids in the 4 weeks preceding enrollment.

Clinical data

Clinical and laboratory data were obtained from the CAVS-MS pilot study database. Participants were enrolled from the following institutions: Cedars-Sinai Medical Center, Cleveland Clinic, Johns Hopkins University, University of California San Francisco, University of Southern California, University of Texas Health Science Center at Houston, University of Toronto - St. Michael's Hospital, University of Vermont, and Yale University. Clinical data included age, sex, race, ethnicity, timing and clinical manifestations of initial symptom onset, timing and manifestations of relapses (if any), and brain and available cervical and thoracic spinal cord MRI findings. CSF testing for OCB was performed in local clinical labs and results showing either the presence or absence of serum-unmatched CSF OCB (≥2 bands) were entered into the CAVS database. Additionally, scores or results from commonly used MS disability measures from the initial study assessment were also included: Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25-FW), dominant and non-dominant 9-Hole Peg Test (9-HPT), Symbol Digit Modalities Test (SDMT), and binocular low-contrast visual acuity (LCVA) at 2.5% and 1.25%. The diagnosis of MS or an alternative condition was confirmed independently by 3 investigators (2 neurologists and an additional neurologist/neuroradiologist) based on the 2017 McDonald criteria. The diagnostic impression was confirmed at 12-month follow-up by site investigators based on clinical data in the electronic medical record.

Image acquisition

Brain imaging was obtained on a standardized protocol using 3-tesla MRI machines at all sites (7 sites with Siemens scanners and 3 sites with Philips scanners), as previously described (Supplemental table 1).[18,19] T2-weighted FLAIR, T2*-weighted segmented EPI, and T1-weighted imaging were obtained with a 3D acquisition. Gadolinium-based postcontrast sequences included T1-weighted and T2*-weighted segmented EPI. Automated postprocessing was used to generate FLAIR* images by coregistration, interpolation, and multiplication of FLAIR and T2*-weighted sequences as previously described.[10,18,19]

Image analysis

As published previously,[18,19] a central rater (LD), blinded to clinical data including MS diagnosis, used imaging data to determine number of T2 lesions, number of CVS positive lesions, and percentage of CVS positive lesions for all participants. In addition to central rater assessment, simplified CVS methods (counting up to 6 CVS positive lesions per scan) were applied by partially blinded site investigators (neurologists with expertise in MS) on

participant scans conducted at their respective institutions. NAIMS criteria for CVS scoring on FLAIR* was used.[11] At each site, a local neurologist rated Select-3 (at least 3 lesions with CVS) and Select-6 (at least 6 lesions with CVS).[12,13]

Statistical analysis

Baseline clinical and radiological data were tabulated according to OCB status and compared. Continuous data whose distribution was approximately normal based on visual inspection were reported with means and standard deviation and assessed with a t-test, and non-normally distributed data with medians and first and third quartiles, and assessed by bootstrap method (2000 re-samples).[20] Categorical variables were reported as proportions and assessed with chi-square testing or Fisher's exact test if one or more cells had a count of less than 5. Diagnostic performance of OCB, Select-3, and Select-6 as standalone tests, and their combinations (simplified CVS method with OCB), were evaluated for MS at initial assessment and 12-month follow-up, by determining sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Combinations of Select-6 with conventional MRI DIS (according to McDonald 2017 criteria) and OCB with conventional MRI DIS were also evaluated. Contingency tables were used to determine sensitivity and specificity of simplified CVS methods and OCB, as standalone tests, or combinations thereof, for predicting a diagnosis of MS. McNemar's test was applied for comparisons of sensitivities, specificities, PPV, and NPV of diagnostic methods and their combinations. Analyses of the diagnostic performance of OCB and CVS were additionally conducted for a subgroup of participants who presented following their first-time neurologic symptoms evaluated for a clinical attack. P-values (two-tailed tests) are reported up to the third decimal if <0.05 or as <0.001 if lower. Due to the exploratory nature of the study, correction for multiple comparisons was not applied. Statistical analysis was performed in R (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria).

Standard protocol approvals, registrations, and participant consents

The CAVS-MS pilot study was approved by the Institutional Review Board at all included sites and consenting participants were enrolled.

Data availability

Deidentified data not published within this article may be shared at a request of a qualified investigator.

Results

The analysis included 53 participants (37 female, 43 White) from participating institutions (Supplemental table 2). Twenty-five participants (47%) had OCB and 28 (53%) did not. At the initial visit, 24 participants (45%) were diagnosed with MS per 2017 McDonald Criteria. Three additional participants (51% total) had been diagnosed with MS by 12-month follow-up (Supplemental table 3). Most participants presented after neurologic symptoms evaluated for confirmation as a clinical attack (38/53, 72%).

Clinical features based on OCB status

Table 1 shows demographic, clinical, and radiological features of all participants, grouped by OCB status. Age, sex, race, ethnicity, and time since first symptom onset were similar across groups. The median time from symptom onset was 17 months. MS was diagnosed more often in the group with OCB (18/25, 72%) than in those without OCB (6/28, 21%). At 12-month follow-up, three additional participants were diagnosed with MS (21/25, 84%), all of whom had positive OCB. T25-FW, 9-HPT (dominant and non-dominant hand), SDMT, binocular LCVA, and EDSS were similar across groups based on OCB status.

Radiological features based on OCB status

No significant difference was found in the median number of T2 lesions between those with and without OCB (14 vs 16, p=0.64). Based on conventional MRI, there were no substantial differences regarding proportions of those meeting DIS (88% vs 68%, p=0.16), DIT (44% vs 32%, p=0.55), or both (40% vs 29%, p=0.56). Participants with OCB had a greater median number of CVS positive lesions (10 vs 3, p <0.001) and a greater median percentage of CVS positive lesions (67% vs 15%, p <0.001). Scans meeting Select-6 were more common in participants with OCB as compared to those without (68% vs 14%, p<0.001), but there was no statistical difference for scans meeting Select-3 (80% vs 54%, p=0.08).

OCB, Select-3, Select-6, or combination status in relation to diagnosis of MS

The proportion of participants with OCB, Select-3, Select-6, and biomarker combinations at the initial timepoint and at 12-month follow-up based on MS diagnosis are presented in table 2. Most participants with OCB were diagnosed with MS at the initial time point (18/25, 72%) and at 12-month follow-up (21/25%, 84%). A similar observation was noted for Select-3, with MS in 20/35 (57%) at baseline and 22/35 (63%) at 12 months. For Select-6, 17/21 (81%) had MS at baseline and 20/21 (95%) at 12 months. In the case of OCB presence and Select-6 positivity (17 participants), 15 (88%) had MS at baseline and all were diagnosed with MS within 12 months. There were 5 participants who had OCB, but were Select-3 negative, and 3 were ultimately diagnosed with MS (60%). In 8 cases where OCB were present and Select-6 was negative, 4 were diagnosed with MS (50%). Most of those with MRI DIS and Select-6 positive status (19/20, 95%) or MRI DIS and OCB positive status (20/22, 91%) were diagnosed with MS by 12 months.

Diagnostic performance of OCB, simplified CVS methods, and combinations of a simplified CVS method with OCB

Sensitivity, specificity, PPV, and NPV of OCB, simplified CVS methods, and combinations thereof for a diagnosis of MS are presented in table 3. In summary, there were no detectable differences in sensitivities across methods, but OCB (0.76) and Select-6 (0.86) were more specific (p<0.05) than Select-3 (0.48). Similar findings were noted at the 12-month assessment, with Select-6 showing a high specificity as a standalone method (0.96). There were no meaningful differences across standalone methods or combinations for NPV at initial assessment and 12-month follow-up (p>0.05). OCB and Select-6 had superior PPV to Select-3 (0.72 and 0.81 vs. 0.57 respectively, p<0.05). The same was observed at the 12-month assessment, with Select-6 having the highest point estimate (0.95). The

presence of OCB in addition to Select-3 positive status considerably improved specificity (0.86 [combined] vs 0.48 [Select-3 alone] at initial assessment, p=0.001) and PPV (0.80 [combined] vs 0.57 [Select-3 alone] at initial assessment, p<0.05). With presence of both OCB and Select-6, PPV was 100% for a diagnosis of MS by 12-month follow-up (1.00). The combination of Select-6 and MRI DIS performed similarly to the combination of OCB and MRI DIS, with notably high point estimates for specificity at initial time (0.90 vs 0.83, p=0.16) and at 12 months (0.96 vs 0.92, p=0.32). In the subgroup of those who presented following first-time neurologic symptoms evaluated for a clinical attack, Select-6 positivity was associated with an ultimate diagnosis of MS in all cases (Supplemental tables 4 and 5).

CVS status in participants who were diagnosed with MS and met DIT by OCB only

There were 6 participants who met McDonald 2017 DIT only based on presence of OCB. Five were positive for Select-3 (83%) and four were positive for Select-6 (67%).

Discussion

The current study provides a direct comparison of the diagnostic performance of OCB, simplified CVS methods (Select-3 and Select-6), combinations of simplified CVS methods with OCB, and combinations of MRI DIS with Select-6 or OCB. The study population was based on a cohort of participants presenting for a clinical or radiological suspicion of MS, which mimics real world practice at North American academic MS centers. Follow-up data regarding MS diagnosis was available after 1 year. Overall, simplified CVS methods had similar diagnostic performance as OCB, with Select-6 being more specific and showing a greater PPV than Select-3*. In those who met DIT through OCB alone, CVS methods were mostly concordant, 5/6 for Select-3 and 4/6 for Select-6, implying that non-invasive imaging biomarkers can be used to avoid invasive CSF testing in some, but not all, cases. Notably, there were no substantial differences regarding diagnostic performance of MRI DIS with Select-6 when compared to MRI DIS with OCB. When a simplified CVS method was combined with OCB, diagnostic specificity increased. Importantly, the presence of OCB and Select-6 positive status was associated with MS in all cases (Table 2).

There is some variability in the determination of how to rate a scan as “CVS positive”. Manual and automated[21,22] approaches for percentage of CVS positive MRI lesions have been used, and a threshold of 40% is the most studied.[23–26] Some studies suggest thresholds as low as 29–35%[9,27,28] or as high as 50–54%[29,30] could be clinically useful, depending on the cohort studied (normal vs pathologic controls, typical vs atypical MS presentations), and the optimal threshold likely depends on the imaging protocol.

A single study previously reported OCB status and percentage of lesion CVS positivity and found no apparent difference between groups.[24] It was based exclusively on those with red flag MS presentations, and the authors did not report T2-weighted lesion or CVS lesion counts.[24] Our study adds novel data showing that simplified methods of CVS assessment are associated with the presence of OCB. Simplified CVS methods at the previously proposed thresholds,[9,12,13,17] as studied here, are clinically more feasible than percentage-based methods and also show concordance with OCB status. In our study population, those without OCB were less frequently diagnosed with MS, but a considerable proportion

still had at least 3 CVS+ lesions. This resulted in a reduced diagnostic performance for Select-3. On the other hand, Select-6 showed a good balance of sensitivity and specificity, and concordance with OCB was high. Nevertheless, lack of standardized simplified CVS methods, e.g. assessment of randomly selected 3 or 10 lesions, which yields a "CVS positive scan" if at least 2/3 or 6/10 selected lesions contain a central vein,[24] limits direct comparability to previous studies. In our study, most participants who were Select-6 positive were also diagnosed with MS at initial assessment, but there were three Select-6 positive participants who were newly diagnosed after 12-months. This observation supports Select-6 and its value as a biomarker with specificity and good PPV appropriate for earlier and accurate diagnosis of MS.

Although the current study contributes to the literature on CVS diagnostic performance and OCB status, there are some limitations. The sample was limited to participants who had CSF sampling done as part of clinical workup separate from study protocol, so a degree of selection bias is present, and may imply some atypical features may have been overrepresented. Additionally, OCB status is not used as a sole factor to diagnose MS in standard clinical practice. Further, unlike MRI acquisition, CSF analysis was conducted per local standards of care and as such is subject to variability of different laboratory methodologies. Standardized CSF acquisition with assays performed at a central lab for not only OCB but also the IgG Index would control for this variability. Our study focused on OCB and other CSF biomarkers such as kappa free light chains and soluble CD27 that were shown to have comparable diagnostic accuracy to OCB were not assayed.[31] Finally, follow-up time was restricted to 12 months.

As biomarkers, OCB and CVS are substantiated by our current understanding of MS pathophysiology;[32,33] however, further validation of the utility of this measure is forthcoming from ongoing studies. Since the completion of CAVS-MS pilot study, two subsequent observational clinical studies were started, which are poised to provide more data on the topic of CVS and OCB in the context of establishing a diagnosis of MS. One of them is the larger multicenter North American CAVS-MS study (NCT04495556), which has recruited 400 participants with equal distribution of typical and atypical presentations, who will be followed over 24 months; CSF data from clinical practice will be recorded.[34] The other one is the United Kingdom-based Diagnose Using the Central Vein Sign (DECISIve, NCT04024969), which is recruiting 115 participants presenting with typical CIS, but not meeting 2017 McDonald, and who will undergo neuroimaging and lumbar puncture per protocol. Since OCB have a predictive value for assessing development of CIS in radiologically isolated syndrome (RIS),[35] the potential utility of CVS as a diagnostic imaging biomarker for such presentations may also become apparent. Ultimate translation to broad clinical practice would require greater availability of 3D T2*-weighted segmented EPI and the automated post-processing tool which generates FLAIR* images, as well as implementation of equivalent methods to more widely used 1.5T MRI.

This study provides data on the diagnostic performance of CVS compared with OCB for MS. In most cases, OCB status and CVS status were concordant and diagnostic accuracy for MS was similar. Future studies should prospectively evaluate the role of CVS as a

replacement for or complement to OCB in RIS, CIS, and atypical presentations of MS, with more extended periods of follow-up time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic, clinical, and radiological data of study participants at the time of initial assessment.

	n		p-value
Variable	**OCB present**	**OCB absent**	
Participants	25	28	
Demographics			
Age (median years, Q1, Q3)	39 [33, 52]	46 [34, 50]	0.293[a]
Sex (female)	16 (64.0%)	21 (75.0%)	0.568[b]
Race			0.169[b]
White	19 (76.0%)	24 (85.7%)	
African American or Black	3 (12.0%)	0 (0.0%)	
American Indian or Alaska Native	1 (4.0%)	0 (0.0%)	
Asian	0 (0.0%)	2 (7.1%)	
Unknown	2 (8.0%)	2 (7.1%)	
Latinx ethnicity	3 (12.0%)	3 (10.7%)	1.000[b]
Weeks since first symptom onset (median, Q1, Q3)	70 [19,282]	66 [24,264]	0.984[a]
Typical syndrome at presentation	4 (16.0%)	7 (25.0 %)	0.640[b]
Clinically isolated syndrome at initial visit	3 (12.0%)	5 (17.9%)	0.833[b]
MS diagnosis at initial visit	18 (72.0%)	6 (21.4%)	0.001[b]
MS diagnosis at 12-month follow-up	21 (84.0%)	6 (21.4%)	<0.001[b]
Clinical assessment at initial visit			
Timed 25-Foot Walk (mean time in s, SD)	5.02 (1.13)	5.20 (1.54)	0.645[c]
Dominant 9-HPT (mean time in s, SD)	20.78 (3.87)	21.33 (3.31)	0.585[c]
Non-dominant 9-HPT (mean time in s, SD)	22.55 (4.31)	21.10 (3.75)	0.196[c]
SDMT (mean n correct, SD)	49.88 (11.42)	51.93 (12.14)	0.535[c]
Binocular LCVA at 2.5% (mean n correct, SD)	39.08 (8.11)	35.82 (8.07)	0.034[c]
Binocular LCVA at 1.25% (mean n correct, SD)	27.77 (12.11)	26.50 (9.38)	0.691[c]
EDSS (median, Q1, Q3)	1.50 [1,2]	1.25 [1,2]	0.549[a]
Radiological assessment at initial visit			
Number of T2 lesions (median, Q1, Q3)	14 [10,24]	16 [4,38]	0.636[a]
Dissemination in space by MRI	22 (88.0%)	19 (67.9%)	0.155[b]
Dissemination in time by MRI	11 (44.0%)	9 (32.1%)	0.545[b]
Dissemination in space and time by MRI	10 (40.0%)	8 (28.6%)	0.558[b]
Number of CVS positive lesions (median, Q1, Q3)	10 [3, 14]	3 [1,4]	<0.001[a]
Percentage of CVS positive lesions (median, Q1, Q3)	67 [50,84]	15 [6,51]	0.010[a]
Select-3 positive	20 (80.0%)	15 (53.6%)	0.079[b]

	n		p-value
Variable	**OCB present**	**OCB absent**	
Select-6 positive	17 (68.0%)	4 (14.3%)	<0.001 *b*

a – bootstrap median difference

b – chi-square or Fisher's exact test

c – t-test

Abbreviations: 9-HPT – 9-Hole Peg Test; CVS – central vein sign; EDSS – Expanded Disability Status Scale; LCVA – low contrast visual acuity; MRI – magnetic resonance imaging; MS – multiple sclerosis; OCB – serum-unmatched oligoclonal bands in cerebrospinal fluid; SD – standard deviation; Q1/3 – first/third quartile

Table 2.

Biomarker results for participants diagnosed with multiple sclerosis at initial assessment and at 12-month follow-up.

Variable	n/total per variable	
	MS diagnosis at initial visit (24/53)	MS diagnosis at 12 months (27/53)
OCB positive	18/25 (72%)	21/25 (84%)
Select-3 positive	20/35 (57%)	22/35 (63%)
Select-6 positive	17/21 (81%)	20/21 (95%)
OCB positive and Select-3 positive	16/20 (80%)	18/20 (90%)
OCB positive and Select-3 negative	2/5 (40%)	3/5 (60%)
OCB positive and Select-6 positive	15/17 (88%)	17/17 (100%)
OCB positive and Select-6 negative	3/8 (38%)	4/8 (50%)
Select-6 positive and MRI DIS	17/20 (85%)	19/20 (95%)
OCB positive and MRI DIS	17/22 (77%)	20/22 (91%)

Abbreviations: MRI DIS – dissemination in space on magnetic resonance imaging (according to McDonald 2017 criteria); MS – multiple sclerosis; OCB – serum-unmatched oligoclonal bands in the cerebrospinal fluid

Table 3.

Sensitivity, specificity, positive and negative predictive values of Select-3, Select-6, oligoclonal bands, or combinations, for diagnosis of multiple sclerosis.

	Sensitivity	Specificity	PPV	NPV
Diagnosis of multiple sclerosis at initial assessment				
OCB	0.75 (0.53, 0.90)	0.76 (0.56, 0.90)	0.72 (0.51, 0.88)	0.79 (0.59, 0.92)
Select-3	0.83 (0.63, 0.95)	0.48 (0.29, 0.67)	0.57 (0.39, 0.74)	0.78 (0.52, 0.94)
Select-6	0.71 (0.49, 0.87)	0.86 (0.68, 0.96)	0.81 (0.58, 0.95)	0.78 (0.60, 0.91)
Select-3 + OCB	0.67 (0.45, 0.84)	0.86 (0.68, 0.96)	0.80 (0.56, 0.94)	0.76 (0.58, 0.89)
Select-6 + OCB	0.62 (0.41, 0.81)	0.93 (0.77, 0.99)	0.88 (0.64, 0.99)	0.75 (0.58, 0.88)
Select-6 + MRI DIS	0.71 (0.49, 0.87)	0.90 (0.73, 0.98)	0.85 (0.62, 0.97)	0.79 (0.61, 0.91)
OCB + MRI DIS	0.71 (0.49, 0.87)	0.83 (0.64, 0.94)	0.77 (0.55, 0.92)	0.77 (0.59, 0.90)
p-values				
OCB vs Select-3	0.157	0.005	0.015	0.890
OCB vs Select-6	0.317	0.083	0.117	0.876
Select-3 vs Select-6	0.083	0.001	0.003	0.957
Select-3 + OCB vs Select-3	0.046	0.001	0.004	0.765
Select-6 + OCB vs Select-6	0.157	0.157	0.232	0.337
Select-3 + OCB vs Select-6 + OCB	0.317	0.157	0.191	0.750
Select-6 + MRI DIS vs OCB + MRI DIS	-	0.157	0.141	0.189
Diagnosis of multiple sclerosis at 12-month follow-up				
OCB	0.78 (0.58, 0.91)	0.85 (0.65, 0.96)	0.84 (0.64, 0.95)	0.79 (0.59, 0.92)
Select-3	0.81 (0.62, 0.94)	0.50 (0.30, 0.70)	0.63 (0.45, 0.79)	0.72 (0.47, 0.90)
Select-6	0.74 (0.54, 0.89)	0.96 (0.80, 1.00)	0.95 (0.76, 1.00)	0.78 (0.60, 0.91)
Select-3 + OCB	0.67 (0.46, 0.83)	0.92 (0.75, 0.99)	0.90 (0.68, 0.99)	0.73 (0.54, 0.87)
Select-6 + OCB	0.63 (0.42, 0.81)	1.00 (0.87, 1.00)	1.00 (0.80, 1.00)	0.72 (0.55, 0.86)
Select-6 + MRI DIS	0.70 (0.50, 0.86)	0.96 (0.80, 1.00)	0.95 (0.75, 1.00)	0.76 (0.58, 0.89)
OCB + MRI DIS	0.74 (0.54, 0.89)	0.92 (0.75, 0.99)	0.91 (0.71, 0.99)	0.77 (0.59, 0.90)
p-values				
OCB vs Select-3	0.317	0.003	0.004	0.271
OCB vs Select-6	0.317	0.083	0.090	0.877
Select-3 vs Select-6	0.157	0.001	0.001	0.377
Select-3 + OCB vs Select-3	0.046	0.001	0.002	0.943
Select-6 + OCB vs Select-6	0.083	0.317	0.317	0.124
Select-3 + OCB vs Select-6 + OCB	0.317	0.157	0.157	0.831
Select-6 + MRI DIS vs OCB + MRI DIS	0.317	0.317	0.337	0.501

Abbreviations: MRI DIS – dissemination in space on magnetic resonance imaging (according to McDonald 2017 criteria); NPV – negative predictive value; OCB – serum-unmatched oligoclonal bands in cerebrospinal fluid; PPV – positive predictive value. Estimates provided as proportions with 95% confidence intervals.