Supplementary Online Content

Sinnecker T, Clarke MA, Meier D, et al; MAGNIMS Study Group. Evaluation of the central vein sign as a diagnostic imaging biomarker in multiple sclerosis. *JAMA Neurol.* Published online August 19, 2019. doi:10.1001/jamaneurol.2019.2478

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Overview on MRI Protocol and Multicenter Design

Center	GRE sequence			IR sequence		Study participants
	type	resolution (mm)	TE/TR (ms)	type	resolution (mm)	
Amsterdam	SWI	0.49x0.49x3.0	23/31	3-D FLAIR	0.98x0.98x1.2	RRMS, n=40
Barcelona	SWI	0.65x0.65x3.0	24.6/33	TIRM, tra	0.49x0.49x2.99	CIS, n=29 RRMS, n=2 Migraine, n=20 SVD, n=24 SLE, n=7
Berlin	SWI	0.78x0.78x3.0	24.6/33	3-D FLAIR	0.98x0.98x1.0	CIS, n=2 RRMS, n=28 NMOSD, n=44
Graz	SWI	0.9x0.9x4.0	59/68	TIRM, tra	0.86x0.86x3.0	CIS, n=73 RRMS, n=71 SVD, n=102
Nottingham	T2*w	0.55x0.55x1.05 with 1.05 gap	25/150	3-D FLAIR	1.0x1.0x1.0	RRMS, n=15 SVD, n=15
Poznan	SWI	0.86x0.86x1.5	20/28	3-D FLAIR	0.49x0.49x1.0	RRMS, n=73 SLE, n=18 SVD, n=22
Siena	SWI	0.3x0.3x1.0	13.4/31	3-D FLAIR	1.0x1.0x1.0	RRMS, n=15 Migraine, n=9

						Cluster headache, n=5
Verona	SWI	0.55x0.55x0.55	29/51	3-D FLAIR	1.0x1.0x1.0	CIS, n=19 RRMS, n=13 Migraine, n=1 NMOSD, n=1

Key: GRE: gradient echo, IR: inversion recovery, TE: echo time, TR: repetition time, TI: inversion time, SWI: susceptibility weighted imaging, T2*w: T2* weighted imaging, FLAIR: fluid attenuated inversion recovery.

eTable 2. Sensitivity and Specificity of the Central Vein Sign at SWI and T2*w

Marker	SWI Specificity	SWI Sensitivity	T2* Specificity	T2* Sensitivity
20% threshold	71.8%	83.8%	80.0%	100.0%
25% threshold	77.2%	79.2%	86.7%	100.0%
30% threshold	78.5%	75.0%	86.7%	100.0%
35% threshold	82.6%	66.6%	86.7%	100.0%
40% threshold	83.9%	59.4%	86.7%	100.0%
45% threshold	85.9%	56.8%	86.7%	100.0%
50% threshold	89.9%	44.5%	86.7%	86.7%
1 CVS lesion	56.4%	90.9%	40.0%	100.0%
2 CVS lesions	81.2%	75.0%	60.0%	100.0%
3 CVS lesions	90.6%	60.4%	73.3%	93.3%
4 CVS lesions	96.0%	48.4%	80.0%	86.7%
5 CVS lesions	99.3%	39.0%	86.7%	80.0%
1 JC CVS lesion	87.9%	32.1%	86.7%	40.0%
2 JC CVS lesions	98.0%	13.3%	100.0%	40.0%
3 JC CVS lesions	100.0%	4.5%	100.0%	20.0%
4 JC CVS lesions	100.0%	2.6%	100.0%	13.3%
1 PV CVS lesion	85.2%	70.5%	80.0%	100.0%
2 PV CVS lesions	98.0%	45.5%	93.3%	93.3%
3 PV CVS lesions	100.0%	27.9%	100.0%	60.0%
4 PV CVS lesions	100.0%	13.0%	100.0%	53.3%
2 PV or JC CVS lesions	70.5%	78.6%	80.0%	100.0%

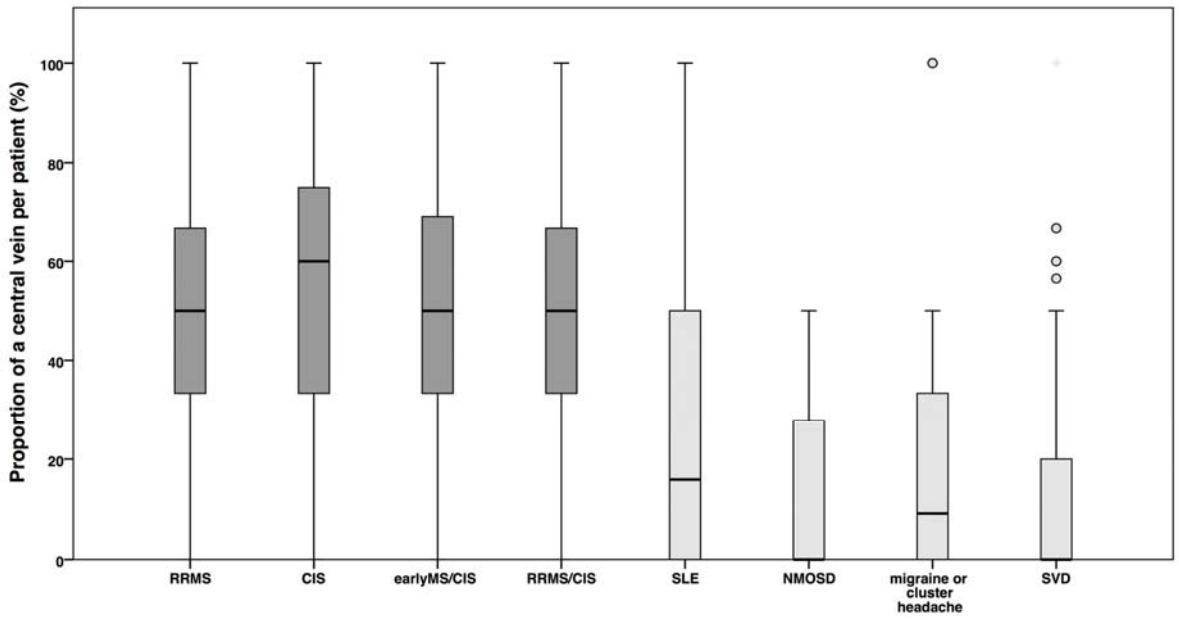
2 PV or JC CVS lesions or 35% threshold	56.4%	91.9%	73.3%	100.0%
2 CVS lesions or 35% threshold	63.1%	86.4%	60.0%	100.0%
3 CVS lesions or 35% threshold	67.8%	82.1%	73.3%	100.0%

Observed sensitivity and specificity values for the central vein sign in differentiating CIS/MS from non-MS are plotted for a SWI and T2*w sequence respectively. Please note that the T2*w group only comprised a very small sample size of 30 participants. SWI and T2*w had a comparable specificity. The sensitivity was much higher when a T2*w sequence was used for the detection of a central vein.

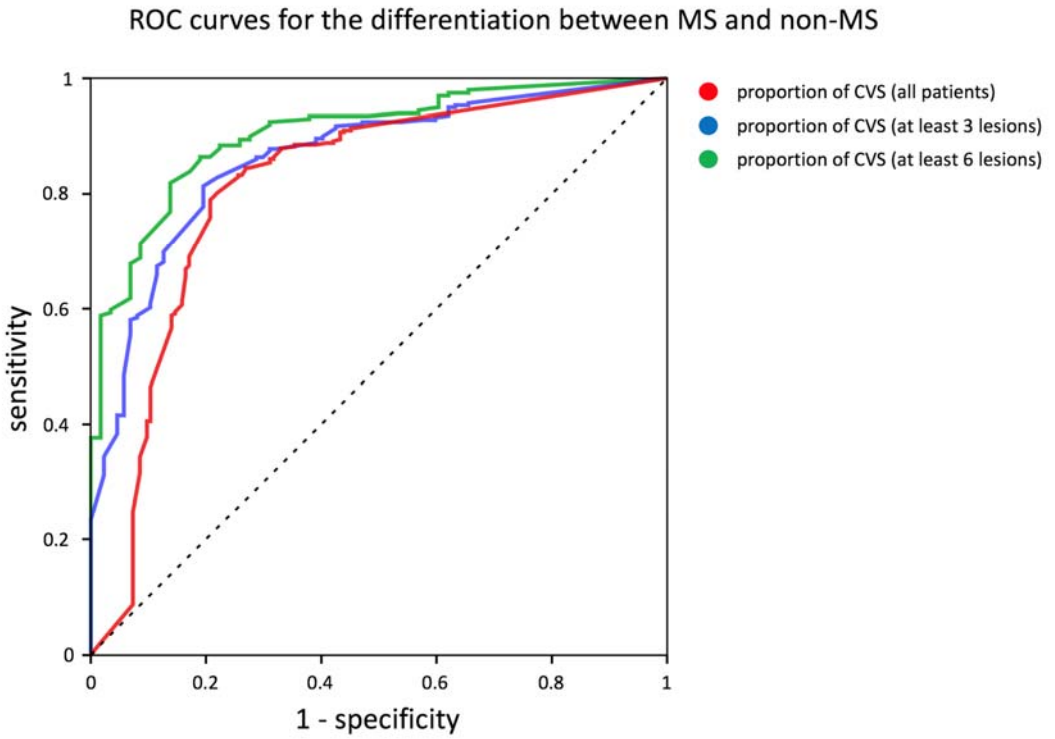
Key: CVS: positive central vein sign, JC: juxtacortical, PV: periventricular.

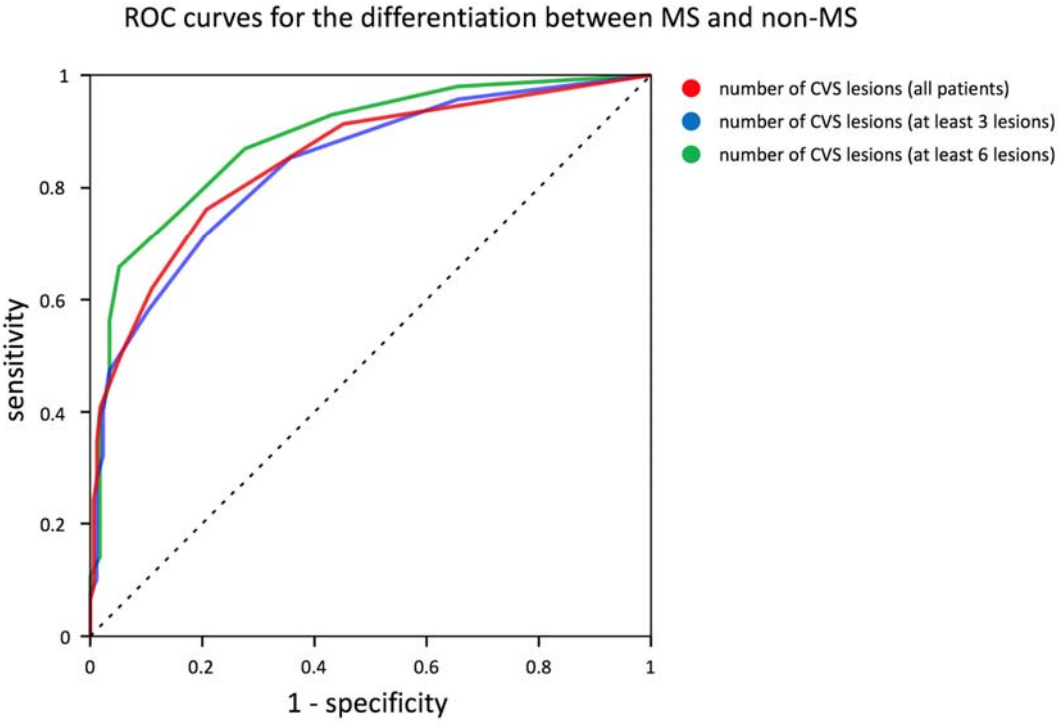
eFigure 1. Box Plot

The proportion of lesions with a central vein per subject is plotted for different disease subgroups.



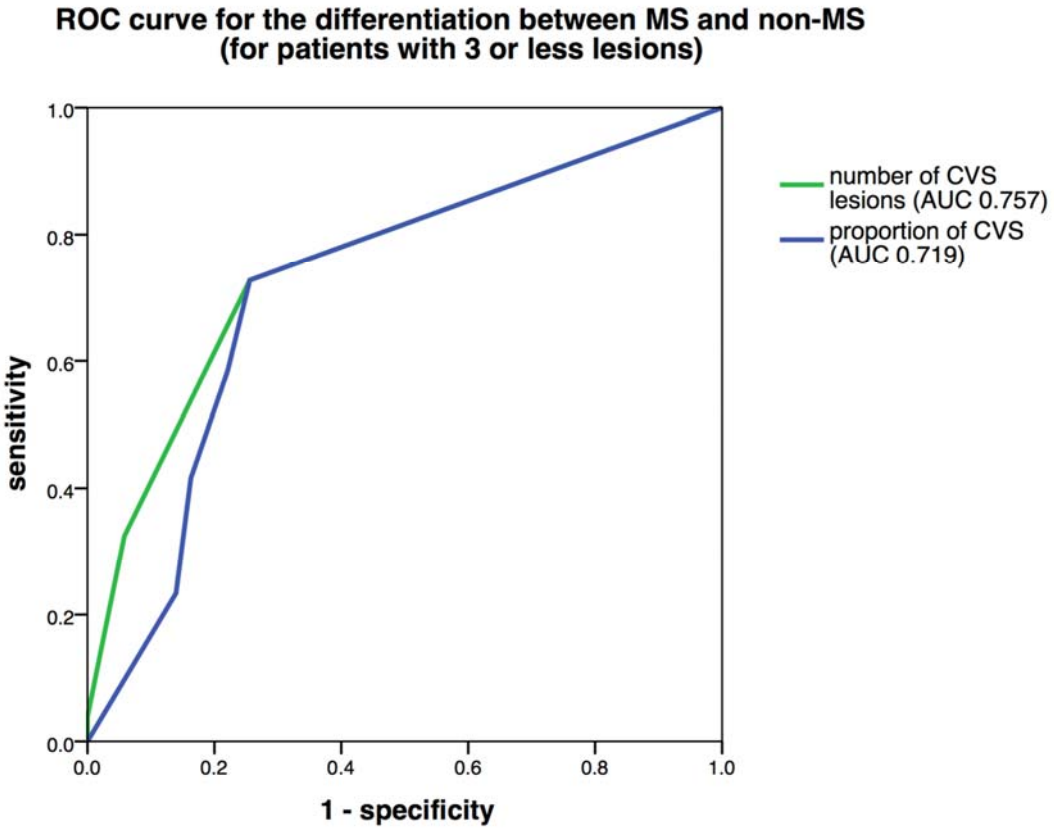
eFigure 2. ROC Curves for the Differentiation Between MS and Non-MS





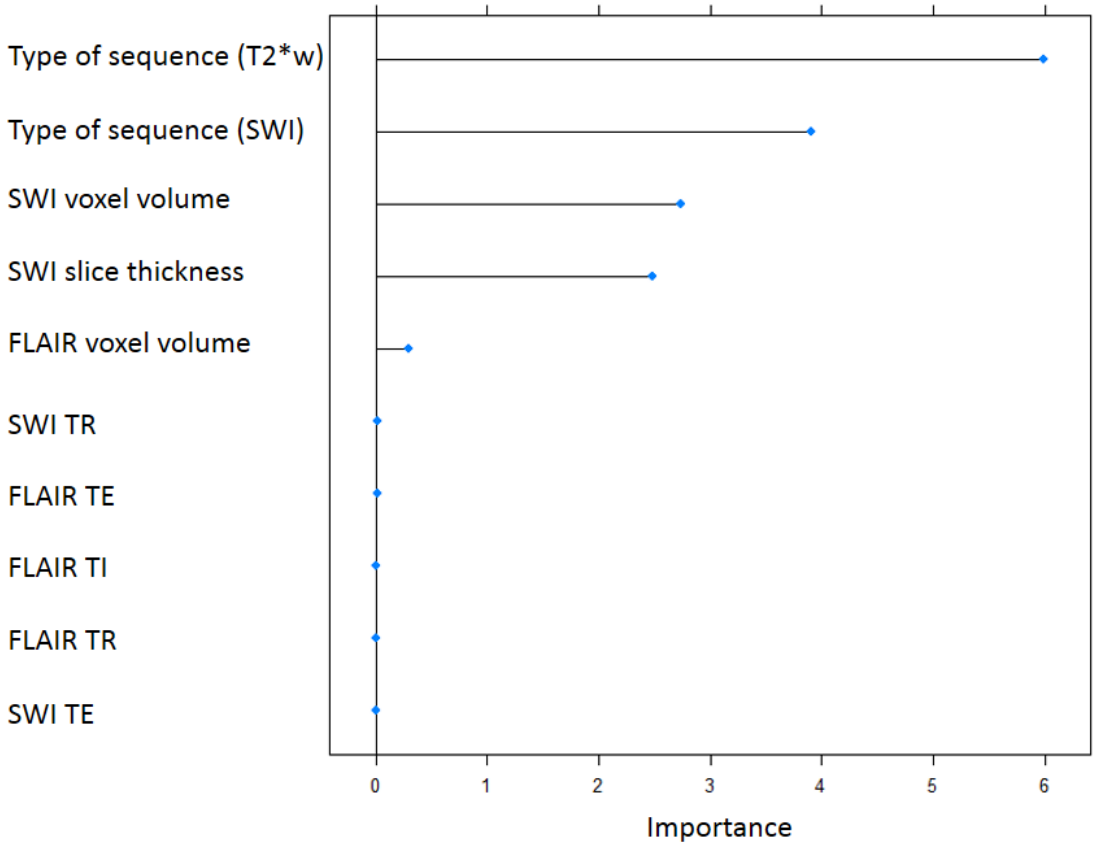
ROC curves for the differentiation between MS and non-MS by using the proportion (top) or number (bottom) of CVS lesions are shown. The graphs illustrate a higher specificity for proportion-based but not lesion-based CVS criteria when at least 3 or 6 lesions were analyzed per participant. Key: ROC: receiver operating characteristic. MS: multiple sclerosis.

eFigure 3. ROC Curves for the Differentiation Between MS and Non-MS in Patients With Three or Less Lesions



ROC curves for the differentiation between MS and non-MS are shown. The graphs illustrate a higher specificity for lesion-based versus proportion-based CVS criteria in patients with only three or less lesions. AUC: area under the curve.

eFigure 4. LASSO Regression Analysis



A LASSO regression analysis was used to identify a potential influence of gradient echo sequence type, voxel volume, slice thickness, TR or TE on the agreement between the clinical diagnosis and 35%-proportion-based CVS criteria (dependent variable). The figure illustrates the estimated contribution of variables (y-axis) on the dependent variable. An importance value (x-axis) above zero indicates a significant contribution to the model. Thus, the type of the gradient echo sequence, SWI voxel volume, SWI slice thickness, and FLAIR voxel volume contributed significantly to the statistical model that together explained approximately 12% of the variance. Key: The importance value reflects the magnitude of the contribution of a given variable to the statistical model.