Quantitative susceptibility mapping for differentiating multiple sclerosis from cerebral small vessel disease

Key points

- Compared to the SVD lesions, MS lesions demonstrate significantly higher susceptibility values, more hyperintense rims, and central vein signs on QSM.

- Magnetic susceptibility measured using QSM allows accurate differentiation of MS from SVD patients.

Authors

Mingjia Hou, Yan Zhang, Ajay Gupta, Susan A. Gauthier, Yi Wang, Weiwei Chen

Correspondence

chenweiwei_tjh@tjh.tjmu.edu.cn (W. Chen),
Tel.: (+86) 027-83663357
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Mingjia Hou, Yan Zhang, Ajay Gupta, Susan A. Gauthier, Yi Wang, Weiwei Chen

Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, Wuhan 430030, China
Department of Radiology, Weill Cornell Medical College, New York, NY 10022, USA
Department of Neurology, Weill Cornell Medical College, New York, NY 10022, USA
Department of Biomedical Engineering, Cornell University, Ithaca, NY, USA

Correspondence: chenweiwei_tjh@tjh.tjmu.edu.cn (W. Chen), Tel.: (+86) 027-83663357

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Abstract

Background and Purpose: With the increasing prevalence of cerebrovascular risk factors in young adults, accurate differentiation of multiple sclerosis (MS) from cerebral small vessel disease (SVD) remains challenging because of the significant overlap in the appearance of white matter lesions on conventional magnetic resonance (MR) images. The purpose of this study was to use quantitative susceptibility mapping (QSM) to differentiate patients with MS from patients with SVD.

Materials and Methods: Thirty-two patients with relapsing-remitting MS and 40 patients with SVD were selected in this institution review board-approved retrospective study. All patient examinations included QSM and T2-weighted FLAIR (T2w). All T2w hyperintense lesions were analyzed on QSM for susceptibility relative to normal-appearing white matter and were evaluated for the presence of hyperintense rims and the central vein sign. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of differentiating MS patients from SVD patients.

Results: The mean susceptibility value of SVD lesions was significantly lower than MS lesions (2.31 ± 9.68 ppb vs. 27.77 ± 20.27 ppb, p < 0.001). Of MS patients and MS lesions, 68.8% and 22.2% had hyperintense rims on QSM, respectively. Of MS patients and MS lesions, 75% and 37.6% had a central vein sign on QSM, respectively. Lesion susceptibility values allowed accurate differentiation MS from SVD with an area under the ROC curve (AUC) = 0.848 for lesion differentiation, AUC = 0.999 for patient differentiation, and an optimal cut-off susceptibility value of 14.88 ppb.

Conclusions: Magnetic susceptibility measured using QSM allows accurate differentiation of MS patients from SVD patients.

Keywords: Multiple sclerosis, Cerebral small vessel disease, Differential diagnosis, Quantitative susceptibility mapping, Susceptibility, Hyperintense rims, Central vein sign

1. INTRODUCTION

An accurate diagnosis of multiple sclerosis (MS) is critically important for effective treatment, but establishing an accurate diagnosis of MS continues to be challenging [1]. A common diagnostic work-up includes differentiation of MS from cerebral small vessel disease (SVD) [1, 2]. SVD is a common cause of stroke, dementia, and functional decline [3], and is characterized on magnetic resonance imaging (MRI) as white matter hyperintensities of presumed vascular origin (SVD-WMHs), lacunes, cerebral microbleeds, enlarged perivascular spaces, and cerebral atrophy [4]. SVD-WMHs are the most common MRI findings, and are sometimes the only findings in SVD patients [3]. SVD-WMHs are similar to multiple sclerosis white matter hyperintensities (MS-WMHs) because
both display neuronal loss, white matter damage, and gliosis [4, 5], and therefore appear similar on conventional MR images.

Typically, MS-WMHs and SVD-WMHs are differentiated based on clinical factors, such as patient age, medical history, lesion morphology, and location. MS commonly affects otherwise healthy young women [1], while SVD generally occurs in older patients with one or more cardiovascular risk factors, such as hypertension, hyperlipidemia, and diabetes. With the increasing incidence of hypertension and diabetes in young adults [6], SVD is now observed in a younger patient population, thus making it difficult to discriminate between MS and SVD [1, 2]. Accurate diagnoses of MS and SVD can be challenging because there can be significant overlap in the appearance of white matter lesions in MS-WMH and SVD-WMH, especially when lesions are not present in those areas highly characteristic of MS, such as periventricular, the cerebellum/brainstem, or the corpus callosum. Distinguishing MS patients from SVD patients is of great clinical significance because of the vastly different treatment strategies and risk factors. Therefore, there is a growing clinical demand to accurately discriminate patients with MS from SVD, especially at the first clinical presentation [1, 2].

Although MS and SVD lesions manifest white matter damage, MS lesions involve macrophage digestion and removal of myelin debris and iron-laden macrophage/macrophage inflammation (often at the lesion rim) that increase MS lesion susceptibility [7-12]. Lesion magnetic susceptibility contrast with surrounding white matter generates a substantial field and manifests as large magnitude hypointensities and large phase clouds on a gradient echo MRI (GRE). Quantitative susceptibility mapping (QSM) eliminates blooming artifacts to reveal the spatial distribution of the magnetic sources, which offers a quantitative assessment of magnetic susceptibility of human tissue and is superior to susceptibility-weighted imaging [13-21]. Compared to MS, SVD exhibits less iron-related inflammation at the site of pathologic demyelination, which led to our hypothesis that iron-related inflammation might be a potential biomarker to distinguish between MS and SVD. Therefore, we propose to use magnetic susceptibility measured on QSM to differentiate MS-WMHs from SVD-WMHs. In this study we aimed to differentiate MS patients from SVD patients using QSM-measured susceptibility values of white matter hyperintensity lesions.

2. MATERIALS AND METHODS

2.1. Patient data

An MRI database in our institution clinical picture archiving and communication system (PACS) was retrospectively reviewed. A total of 32 relapsing remitting MS (RRMS) patients whose MRI examinations included a 3D gradient-echo sequence in the standard-of-care MRI imaging were selected in this institution review board-approved retrospective study. All 32 RRMS patients were clinically confirmed according to the 2017 revisions of the McDonald criteria. Of the 32 patients, there were 23 females and 9 males, with an age range of 22–61 years (mean, 39.3 ± 10.9 years), expanded disability status scale (EDSS) from 0–6 (median, 2), and disease duration from 2–32 years (mean, 7.31 ± 7.05 years). For comparison, 40 SVD patients were recruited in this study using the following criteria: (a) a recent transient ischemic attack with white matter hyperintensities on T2-weighted images; (b) at least one cerebrovascular disease risk (hypertension [blood pressure >140/90 mm Hg or on an antihypertensive medication], diabetes mellitus [a hemoglobin A1C > 6.5% or on a diabetic medication], and hyperlipidemia [low-density lipoprotein >100 mg/dL or on a statin]); and (c) a recent MRI that included a 3D gradient echo sequence. Of the 40 patients, there were 26 females and 14 males, with an age range of 21–69 years (mean, 59.4 ± 8.1 years).

For both MS and SVD patients, MRI was performed with a 3.0-T MRI system (GE Healthcare, Milwaukee, WI) using an 32-channel head coil and the following protocols: (a) T1 weighted-images (T1WI); (b) T2-weighted images (T2WI); (c) T2-weighted fluid attenuated inversion recovery (T2FLAIR); and (d) T2*-weighted spoiled multi-echo gradient echo sequence (GRE). For each MS patient, gadolinium (Gd)-enhanced T1w imaging was also performed. Imaging parameters for the multi-echo GRE sequences were the same as described elsewhere [9]. QSM and GRE magnitude images were reconstructed from the data acquired with the multi-echo GRE sequence using an in-house software implemented in C++ [22]. The entire reconstruction was fully automatic without any user intervention to eliminate operator bias. The data from all eight echoes acquired in the multi-echo GRE sequences were used with a spherical mean value operation, a lambda value of 1000, and a default kernel size of 5 mm. All images of different sequences were co-registered using the FMRIB Linear Image Registration Tool [FLIRT] [23]. GRE magnitude images and QSM were derived from the same multi-echo GRE sequence, and thus co-registered for each patient.

2.2. Imaging analysis

T2-hyperintense lesions were assumed to be MS-WMH in RRMS patients [1]. The presence of a central vein sign (CVS) containing deoxyhemoglobin on QSM was also identified for the diagnosis of MS [2, 24]. T2-hyperintense lesions with T1-isointensity or -hypointensity, but without cavitation were assumed to be SVD-WMH in SVD patients [4]. White matter regions without an abnormal signal on T1w, T2w, T2FLAIR, and post-Gd T1wI were assumed to be normal-appearing white matter (NAWM).

First, lesions were characterized on QSM based on radiologic impression. All MR images of MS and SVD patients were reviewed by two neuroradiologists (Reader 1 and Reader 2 with 1 and 10 years of experience, respectively) who were blinded to the patients’ clinical information.
and diagnoses. All differences were resolved by consensus. All boundaries identified on MS-WMHs and SVD-WMHs were characterized based on the following: signal intensity of an entire lesion on QSM (hyperintense, hypointense, or isointense relative to NAWM); the presence of a hyperintense rim relative to the center of the lesion on QSM; the appearance of a central vein sign on QSM; identification of cerebral microbleeds on QSM; and visualization of contrast enhancement on post-Gd images. Then, the patients were diagnosed with MS or without MS patients (SVD in this study) according to our hypothesis that a patient was presumed to be an MS patient if the WMHs appeared as hyperintense lesions on QSM, lesions contained hyperintense rims on QSM, or lesions containing a CVS on QSM.

Then, the susceptibility values of all MS-WMHs and SVD-WMHs were measured on QSM. MS-WMH and SVD-WMH three dimensional regions-of-interest (ROIs) were semi-automatically segmented by a neuroradiologist (Reader 3 with 20 years of experience) on the T2FLAIR and QSM images using an in-house OsiriX ROI auto-segmentation tool that has been used in previous studies [25]. If a lesion was inconspicuous on QSM, the ROI on T2FLAIR was overlaid onto the QSM image and manually revised to eliminate inclusion of veins or obvious artifacts. The 3D ROI of a lesion was defined by compounding 2D lesion boundaries segmented on consecutive slices. The NAWM ROI was drawn contralateral to the lesion or on surrounding NAWM when the contralateral area contained another lesion. The susceptibility values of MS-WMHs and SVD-WMHs relative to the corresponding NAWMs were calculated.

2.3. Statistics
Statistical analyses were performed using SPSS software (Windows version 22.0; SPSS, Inc., Chicago, IL, USA). Statistical results are presented as the mean ± SD. Differences in lesion signal intensity on QSM, the presence of a hyperintense rim, the CVS, and cerebral microbleeds between MS and SVD patients were all assessed using a chi-square test. Differences in susceptibility values between MS-WMHs and SVD-WMHs were assessed by a t-test. Receiver operating characteristic (ROC) curve analysis of lesion susceptibility values was used to differentiate MS-WMHs from SVD-WMHs. The area under the ROC curve (AUC) and the best cut-off susceptibility value were estimated, as well as diagnostic accuracy (sensitivity and specificity).

2.4. Causes for misdiagnosis of MS patient analysis
The misdiagnosis of MS patients was further analyzed by another neuroradiologist (Reader 3). To determine the causes for MS patient misdiagnosis, we further calculated the age of MS-WMHs. We accessed all available prior MRI examination in the PACS to form an MRI time course for each MS patient to identify the age of each MS-WMH. All images in the MRI time course were co-registered regardless of the imaging sequences and any MRI time points. We reviewed all images of the MRI time course to determine whether the first appearance MRI of a MS-WMH could be identified, and if so the time point of the first appearance MRI was recorded. The age of a MS-WMH was defined as the time between the MRI of the first lesion appearance and the QSM. The age-determined MS-WMHs were first classified into Gd-enhancing (Gd+) and Gd non-enhancing (Gd-) lesions. Then, the Gd- MS lesions were further categorized into 5-year lesion age intervals. The MS-WMH susceptibility values of different groups were calculated and compared with one-way ANOVA.

| Table 1 | Summary of the characteristics of MS-WMHs and SVD-WMHs on QSM. |
|---|---|---|
| | MS | SVD | P value |
| Number of Patients | 32 | 40 | |
| Gender | 9M/23F | 14M/26F | 0.616 |
| Age (years) | 22-61 (39.3 ± 10.9) | 21-69 (59.4 ± 8.1) | <0.05 |
| Number of lesions | 598 | 483 | |
| Signal intensity of entire WMH on QSM | | | |
| Hyperintense | 446 (74.58%) | 0 (0%) | <0.001 |
| Isointense | 152 (25.42%) | 483 (100%) | <0.001 |
| Hyperintense rim relative to the center of a WMH on QSM | 133 (22.24%) | 0 (0%) | <0.001 |
| Central vein sign on QSM | 225 (37.63%) | 0 (0%) | <0.001 |
| Patients with cerebral microbleeds on QSM | 2 (6.25%) | 29 (72.5%) | <0.001 |

Note. MS-WMHs = Multiple sclerosis white matter hyperintensities, SVD-WMHs = white matter hyperintensities of presumed vascular origin, WMHs = white matter hyperintensities.
3. RESULTS

A total of 598 MS-WMHs were detected in 32 MS patients and 483 SVD-WMHs were detected in 40 SVD patients. The lesion characteristics are summarized in Table 1 and illustrated in Figures 1 and 2. Mild-to-intermediate hyperintense lesions, hyperintense rims, and central vein signs were only found in MS patients.

**Figure 1 | Three representative MS-WMH cases.**

MS-WMHs appear hyperintense on QSM (black and white arrows) with a hyperintense rim (black arrows in c, f, and i) and the central vein sign (black arrowheads in c and f).
Figure 2 | Three representative SVD-WMH cases.
SVD-WMHs appear hyperintense on the T2WI (white boxes in a; black arrowheads in c and e) and isointense on QSM (b, d, and f). Additionally, a cerebral microbleed is identified on QSM (white arrowheads in f).
on QSM. There were significantly fewer cerebral microbleeds in MS patients compared to SVD patients (6.25% vs. 72.5%, p<0.001). The susceptibility values of SVD-WMHS were slightly higher than NAWM (1.58 ± 8.69 ppb, p<0.001). The susceptibility values of MS-WMHS were significantly higher than SVD-WMHS (29.18 ± 19.94 ppb vs. 1.58 ± 8.69 ppb, p<0.001).

The accuracy of differentiating MS patients from SVD patients using the presence of hyperintense lesions on QSM based on radiologic impression was nearly perfect (Table 2), achieving a sensitivity of 96.87% and a specificity of 100%. One MS patient only had isointense lesions on QSM (Figure 3) without microbleeds and was correctly diagnosed by considering the Gd enhancement. The presence of hyperintense rim lesions on QSM for diagnosing MS patients achieved a sensitivity of 68.75% and a specificity of 100%, and the presence of a central vein in lesions on QSM achieved a sensitivity of 75% and a specificity of 100%. For diagnosing MS patients using any of the three signs (hyperintensity, hyperintense rims, or CVSs), the sensitivity was 96.87%, which was also achieved using hyperintensity alone on QSM.

The accuracy for differentiating MS-WMHS from SVD-WMHS using lesion susceptibility values measured on QSM achieved an AUC = 0.852 (95% CI: 0.814–0.886, p<0.001; Figure 4a). At an optimal susceptibility cut-off value of 14.88 ppb, the sensitivity was 73.7% and the specificity was 99.6%. The misclassified MS-WMHS were Gd-enhancing MS-WMHS and old chronic silent MS-WMHS, both of which were QSM isointense (Figure 5). Of 598 detected MS-WMHS in the current study, 152 MS-WMHS in 23 MS patients were identified by age as follows: 8 were Gd+ and 0 years; 115 were Gd+ and ≤ 5 years; and 29 were Gd- and > 5 years. As shown in Figure 3, SVD-WMHS showed significantly lower susceptibility values than MS-WMHS in the Gd+ and ≤ 5-year group (1.58 ± 8.69 ppb vs. 38.43 ± 13.00 ppb, p<0.0001); however, SVD-WMHS showed similar susceptibility value to MS-WMHS in the Gd+ and 0-year group (1.58 ± 8.69 ppb vs. 0.53 ± 3.34 ppb, p=0.765) and MS-WMHS in the Gd- and > 5-year group (1.58 ± 8.69 ppb vs. 4.67 ± 3.18 ppb, p=0.551).

The accuracy for differentiating MS patients from SVD patients using lesion susceptibility value achieved an AUC of 0.999 (95% CI: 0.988–1, p<0.0001; Figure 4b). At an optimal cut-off susceptibility value of 14.88 ppb, the sensitivity was 97.4% and the specificity was 99.6%.

### 4. DISCUSSION

The MS-WMH lesion susceptibility values were significantly higher than the SVD-WMH lesions, while the SVD-WMH lesion susceptibility values were slightly greater than the NAWM. Hyperintense lesions, hyperintense rims, and CVSs were only detected in MS lesions on QSM. The QSM-measured susceptibility values of lesions achieved good accuracy in differentiating MS from SVD lesions with an AUC of 0.852 and excellent accuracy in differentiating MS from SVD patients with an AUC of 0.999. To diagnose MS patients with active lesions (acute or chronic active), the accuracy of radiologic impressions based on the presence of QSM hyperintense lesions was excellent with a sensitivity of 96.87% and a specificity of 100%, and became perfect with Gd-enhancement to capture patients with acute lesions alone.

The excellent accuracy of using QSM to differentiate MS patients against SVD patients represents a marked improvement over other methods, such as using the central vein sign detected on images with susceptibility hypointensity contrast [2, 24]. This diagnostic capability of QSM can be understood from the disease pathogeneses underlying SVD and MS, and lesion magnetisms. SVD and MS are separated by vascular origins. Specifically, SVD originates at the arterial side [26, 27], while MS originates at the venous side [28]. SVD and MS differ in inflammatory components. Only MS lesions involve macrophage digestion and removal of myelin and iron-laden microglia/macrophages inflammation [29].

The pathologic processes underlying SVD and MS and the lesion susceptibility values can be summarized as follows. SVD encompasses a group of age-related neuropathologic processes affecting the small perforating arteries, arterioles, and capillaries in the brain [3, 26, 27, 30]. SVD is categorized into two main forms [3, 4]. The most common form is hypertensive arteriopathy, which refers to non-amyloid degenerative alterations in the vessel walls, including arteriolar sclerosis, fibrinoid necrosis, and lipohyalinosis [27]. These vessel wall alterations

| Table 2 | Diagnostic performance for differentiating MS from SVD patients using radiologic impression of QSM. |
|---|---|---|---|---|
| Hyperintensity on QSM | 96.87% (31/32) | 100% (40/40) | 100% (31/31) | 97.56% (40/41) |
| Hyperintense rim on QSM | 68.75% (22/32) | 100% (40/40) | 100% (22/22) | 80% (40/50) |
| Central vein sign on QSM | 75% (24/32) | 100% (40/40) | 100% (24/24) | 83.33% (40/48) |
| Hyperintensity+hyperintense rim+ central vein sign | 96.87% (31/32) | 100% (40/40) | 100% (31/31) | 97.56% (40/41) |

Note. Data in parentheses are the number of patients. MS = multiple sclerosis, SVD = cerebral small vessel disease, PPV = positive predictive value, NPV = negative predictive value, QSM = quantitative susceptibility mapping.
often present as enlargements of the surrounding perivascular spaces, and sometimes present as microin- farctions, thromboses, or microbleeds. The less common form is cerebral amyloid angiopathy, a chronic degenerative disease characterized by progressive deposition of amyloid-beta in the media and adventitia of small arteries, arterioles, and capillaries in the cerebral cortex, the overlying leptomeninges, and the cerebellum. The affected vessels show secondary vasculopathic changes, such as fibrinoid necrosis, loss of smooth muscle cells, and remodeling.
Figure 4 | The susceptibility value achieved an AUC of 0.852 and the optimal susceptibility cut-off value was 14.88 ppb for differentiating MS-WMHs from SVD-WMHs (a) with a sensitivity of 73.68% and a specificity of 99.6%. However, the susceptibility value achieved an AUC of 0.999 and an optimal susceptibility cut-off value of 14.88 ppb for differentiating MS patients from SVD patients (b) with a sensitivity of 97.39% and a specificity of 99.6%.

Figure 5 | The susceptibility values of SVD-WMHs and MS-WMHs at different Gd enhancement statuses and lesion ages.

wall thickening, formation of microaneurysms, and deposition of perivascular blood breakdown products. Accordingly, SVD MRI manifestations include recent small subcortical infarcts, lacunes, and white matter hyperintensity of presumed vascular origin, perivascular spaces, cerebral microbleeds, and brain atrophy. In particular, WMH lesions in SVD patients on QSM were shown, for the first time, to be isointense. This QSM isointensity of SVD-WMHs suggests that white matter damage in SVD may affect myelin integrity, but preserve myelin content.

In contrast, MS lesions are hyperintense on QSM for years [9] due to myelin digestion and removal by macrophages, and iron accumulation in macrophages and microglia [31-33]. White matter MS lesion formation starts with macrophages and other immune cells infiltrating the transiently open blood-brain barrier [BBB] (Gd-enhancing on T1w). Macrophages immediately tear myelin into fragments and phagocytose myelin fragments [29]. At this acute lesion formation stage with no substantial myelin digestion by macrophages with little departure of myelin-laden macrophages and absence of iron, lesion susceptibility is not altered. As BBB integrity recovers, macrophages have digested myelin substantially and lesion susceptibility has correspondingly increased [33]. Gradually, myelin-laden macrophages in the center of the lesion leave, and microglia/macrophages in the lesion rim become iron-positive [12]. At this stage of early chronic active lesions, myelin debris removal and iron buildup result in a large increase in lesion susceptibility as QSM hyperintensity [often with the presence of QSM hyperintense rims, as found here, in 22.24% of MS lesions and 68.75% of MS patients] [32]. After several years, activities of microglia/macrophages abate, lesions become chronically silent, and appear isointense on QSM as lesion iron content returns to lower than the adjacent NAWM [8, 9, 34]. Based on this time course of changing myelin and iron levels in microglia/macrophages, MRI can accurately diagnose MS patients with active acute inflammation (Gd-enhancing) or active chronic inflammation (QSM hyperintense).

MS lesions are thought to originate from veins and venules favored by immune cells to interact with antigen-presenting cells and to trigger inflammatory attacks, ultimately resulting in the formation of lesions surrounding veins [28]. Accordingly, MS lesion manifestations include CVSs on gradient echo MRI that is sensitive to paramagnetic deoxyheme in the veins [24, 35]. Because deoxyheme in a vein reflects metabolic oxygen consumption by tissues that are drained by the vein, the veins depicted on QSM [36, 37] can represent MS brain tissue function. The deoxyheme level in the central vein or veins connected to MS lesions vary
from lesion-to-lesion and from patient-to-patient, as observed in our study. This varying oxygenation level may be a function of the diverse sensitivities in detecting central veins with qualitative T2*-weighted hypointensity in the CVS literature [24, 35, 38-44]. The heterogeneity in the levels of venous deoxyheme may limit CVS sensitivity in diagnosing MS [24] and complicate the CVS definition on hypointensity contrast [2]. Of greater importance, quantitative investigation of lesion veins using QSM may help us understand the varying metabolic functions and oxygen requirements of regional brain tissue drained by the corresponding vein.

This study focused on white matter hyperintensities on T2-WIs that consistently present in both SVD and MS patients. Other SVD manifestations on MRI include brain tissue drained by the corresponding vein.

In summary, the magnetic susceptibility values of white matter hypointensity lesions measured on QSM allowed accurate differentiation of MS from SVD patients.

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None.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

ABBREVIATIONS

QSM, quantitative susceptibility mapping; RRMS, relapsing-remitting multiple sclerosis; SVD, cerebral small vessel disease; SVD-WMH, white matter hyperintensities in cerebral small vessel disease; MS-WMH, white matter hyperintensities in multiple sclerosis; NAWM, normal-appearing white matter; ROC, receiver operating characteristic; AUC, area under the ROC curve; Gd+ lesions, Gd-enhancing lesions; Gd- lesions, non-enhancing lesions; CVS, central vein signs.

REFERENCES

Original Research


