Clinical Relevance of Improved Microbleed Detection by Susceptibility-Weighted Magnetic Resonance Imaging

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Background and Purpose—Susceptibility-weighted imaging (SWI) has been shown to be more sensitive in detecting cerebral microbleeds (MBs) than is conventional T2*-weighted gradient-recalled echo imaging (GRE). However, the clinical relevance of this improved detection in terms of associations with clinical measures and risk factors is unclear. We sought to determine whether associations of MBs with clinical characteristics, risk factors, white-matter hyperintensities, and lacunes were different on GRE versus SWI in memory clinic patients.

Methods—One hundred forty-one patients presenting at our memory clinic were included and underwent clinical evaluation and a magnetic resonance imaging protocol including both GRE and SWI. Images were analyzed for numbers and locations of MBs and white-matter hyperintensities. In a subset of patients, apolipoprotein E status was determined. Negative binomial regression was used to assess clinical and radiologic associations with MB number.

Results—MB prevalence was 23% on GRE and 40% on SWI. A total of 219 and 284 MBs were detected on GRE and SWI, respectively. Within groups with MBs, the median MB count was 1 (range, 1 to 144) on GRE and 2 (range, 1 to 129) on SWI ($P<0.001$). The increase in the number of MBs on SWI was equally distributed among brain regions. Strengths of the associations with age, sex, white-matter hyperintensities, and presence of lacunes with higher MB numbers were comparable for GRE and SWI (all $P<0.05$); no differential independent associations were detected.

Conclusions—SWI detected more MBs in more patients, irrespective of MB location. However, this enhanced detection had no improved clinical relevance in terms of associations with vascular risk factors or radiologic markers of small-vessel disease. **(*Stroke*. 2011;42:1894-1900.)**

Key Words: cerebral microbleeds ■ MRI ■ susceptibility-weighted imaging ■ Alzheimer disease ■ dementia ■ risk factors ■ leukoaraiosis ■ lacunes

Microbleeds (MBs), seen on T2*-weighted gradient-recalled echo (GRE) magnetic resonance imaging (MRI), are small, rounded, dotlike, hypointense foci. Histologically, MBs represent hemosiderin, likely occurring from leakage through small cerebral vessels and that are contained by surrounding macrophages in the brain parenchyma.[1–4] Clinically, MBs are associated with hypertension, signs of small-vessel disease, ischemic and hemorrhagic stroke, cognitive decline, and mortality in different populations. However, these associations have not been conclusively found across all studies, probably partly due to differences in scanning techniques.[5,6]

Technical developments such as new imaging sequences and higher magnetic field strengths have improved MB detection on MRI in recent years.[6] The recently introduced sequence technique of susceptibility-weighted imaging (SWI) is increasingly being used routinely in the clinical setting, and it maximizes the sensitivity to susceptibility effects by combining a long echo time (TE) and a fully flow-compensated 3D gradient-echo sequence. Furthermore, it uses filtered phase information to enhance the contrast in magnitude images and adds a new source of information, that is, the difference in susceptibility between tissues.[7,8] As a result, MBs are more sensitively detected by SWI compared with GRE.[8–12] A recent study showed that all hypointense lesions visible on postmortem SWI corresponded to angiopathy-related abnormalities (most commonly, acute microhemorrhage, hemosiderin residua of old hemorrhages, and small lacunes ringed by hemosiderin).[2] However, data on the clinical relevance of this improved MB detection in terms of associations with clinical outcome measures and risk factors are rather limited. On MRI, MBs are associated with radiologic signs of small-vessel disease, white-matter hyperintensities (WMHs), and lacunar infarcts.[13–17] Clinically, MBs

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have been quite consistently associated with the vascular risk factors, older age, and chronic hypertension.[5,16,18] Apart from hypertensive vasculopathy, MBs are associated with cerebral amyloid angiopathy (CAA).[6] Although both microangiopathies probably occur frequently in a memory clinic population, CAA has been found in the vast majority of Alzheimer disease (AD) patients,[19] and it may play an important role in our population. As a result, MBs are commonly detected in memory clinic patients.[20] In this population, MBs have been associated with mortality.[21] The relation of MBs with cognition in AD, however, has not yet been determined.[20,22–24] Nevertheless, when MBs are numerous in AD patients, they may contribute to cognitive decline,[25] similar to what is observed in patients with vascular dementia and stroke.[26,27]

In this study, we aimed to determine whether the associations of MBs with clinical characteristics, risk factors, and associated MRI changes were different between GRE and SWI in a memory clinic population.

Methods

Patient Population

From November 2007 to September 2008, a total of 156 consecutive patients presenting at our memory clinic received a 1.5-T MRI scan including both GRE and SWI. Of these patients, 15 were excluded because of missing scans or scans of unacceptable quality for 1 or both sequences. This resulted in a total number of 141 patients with both GRE and SWI sequences of acceptable quality (mean age, 62±9 years; 57% male).

All patients underwent standardized dementia screening, including a medical history; physical, neurologic, and neuropsychological examinations; and MRI. Dementia severity was assessed with the Mini-Mental State Examination.[28] Patients were considered as having arterial hypertension, diabetes mellitus, and hypercholesterolemia if they had a known history of the disease or were receiving drug treatment for these conditions. Furthermore, screening involved routine laboratory examinations. Diagnoses were made in a multidisciplinary consensus meeting. Diagnoses of probable AD (n=49) were made according to the clinical criteria of the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[29] and a diagnosis of mild cognitive impairment (n=16) was based on Petersen criteria.[30] When all clinical investigations were normal, patients were considered to have subjective complaints (n=20). The subgroup of other dementias (n=18) included various diagnoses such as frontotemporal lobar degeneration (n=7),[31] dementia with Lewy bodies (n=5),[32] and other neurodegenerative disorders (n=6). The subgroup of other disorders (n=38) included patients with other neurologic disorders, including stroke (n=9), psychiatric disorders (n=18), and unclear diagnoses (n=11). The study was approved by the ethics review board of the Vrije Universiteit University Medical Center Amsterdam, and all subjects gave written, informed consent for their clinical data to be used for research purposes.

MRI Protocol

MRI was performed on a 1.5-T whole-body MRI system (Sonata Syngo, Siemens Medical Systems, Erlangen, Germany), with an 8-channel phased-array head coil. The imaging protocol included the following pulse sequences: (1) axial T2*-weighted GRE (21 slices, field of view=250 mm, in-plane voxel size=1×1 mm, slice thickness=5 mm, interslice gap=1.5 mm, repetition time [TR]=415 ms, TE=25 ms, flip angle=15°); (2) axial SWI (44 slices per slab, field of view=250 mm, voxel size=1×1×2 mm, TE=40 ms, TR=48 ms, flip angle=15°). SWI images were constructed by multiplying magnitude images with filtered phase images to enhance the susceptibility effect, and then a minimum-intensity projection reconstruction was performed with a slice thickness of 6 mm and an interslice gap of 2 mm; (3) coronal T1-weighted 3D magnetization-prepared rapid-acquisition gradient-echo volumes (single slab, 176 sections, voxel size=1×1×1.5 mm; TR=2700 ms, TE=5.2 ms, inversion time=950 ms; flip angle=8°); (4) axial 2D fluid-attenuated inversion recovery (42 slices, in-plane voxel size=1×1 mm, slice thickness=5 mm, interslice gap=1.5 mm, TE=108 ms, TR=9000 ms, inversion time=2500 ms); and (5) axial T2-weighted turbo spin-echo (23 slices, in-plane voxel size=0.6×0.6 mm, slice thickness=5 mm, interslice gap=1.5 mm, TE=114 ms, TR=4590 ms).

Image Analysis

MBs were rated by 1 observer. MBs were defined as rounded, hypointense homogeneous foci up to 10 mm in size on GRE and SWI sequences.[20] Lesions in sulci probably representing flow voids from vessels and lesions in the globus pallidus, supposedly representing iron or calcium deposits, were not considered. Choroid plexus and pineal calcifications were also not considered, as were lesions suggestive of partial-volume effects.

The assessment of MBs was performed according to their anatomic location (lobar or nonlobar). Lobar MBs were allocated to 1 of 4 lobes: frontal, parietal, occipital, and temporal. MBs in the basal ganglia including the thalamus were scored as nonlobar. Patients with multiple, strictly lobar MBs were considered as probable CAA patients, analogous to the Boston criteria.[33] Owing to the difference in coverage of scanning between the 2 sequences at the brainstem level, infratentorial MBs were not taken into account.

In a first step, MBs of 20 patients were assessed and counted on both sequences by 3 observers with different levels of experience with MRI, who were blinded to the clinical data of interest (J.D.C.G., 2 years' experience; M.P.W., 9 years' experience; F.B., 22 years' experience) for interobserver reliability purposes. All raters were blinded to any clinical and paraclinical information. First, all GRE images were randomly presented and analyzed. Second, SWI images were rated, with blinding to MB scores on GRE. After >2 months, an MB recount of those 20 scans was performed by reader 1 (J.D.C.G.) to assess intraobserver reliability. Subsequently, the remaining scans were rated by a single rater (J.D.C.G.) in the same fashion.

In addition, WMHs were visually assessed from the fluid-attenuated inversion-recovery sequence according to the modified Fazekas rating scale.[34] The scale ranges from 0 to 3 (none, punctuate, early confluent and confluent). Furthermore, the presence of large-vessel and lacunar infarcts was assessed. Large-vessel infarcts were rated as present or absent, based on hyperintensity of the lesion on both fluid-attenuated inversion-recovery and T2-weighted sequences. Lacunar infarcts were defined as well-demarcated lesions from 3 to 15 mm, with a cerebrospinal fluid-like signal on all sequences.

Statistical Analysis

For statistical analysis, SPSS 15.0 for Windows (SPSS, Chicago, IL) and STATA version 11 (Stata Corp, College Station, TX) were used. The degree of agreement was defined according to the method of Landis and Koch with weighted Cohen's kappas,[35] as follows: for slight agreement, the kappa value ranged from 0.00 to 0.20; for fair agreement, the kappa value ranged from 0.21 to 0.40; for moderate agreement, the kappa value ranged from 0.41 to 0.60; for substantial agreement, the kappa value ranged from 0.61 to 0.80; and for excellent agreement, the kappa value ranged from 0.81 to 1.00. Categorical data were analyzed by χ^2 tests. Comparison between groups for continuous variables was executed by Student *t* tests or Mann–Whitney *U* tests when appropriate. For the difference in MB detection between the 2 sequences, Wilcoxon signed-rank tests were used. Negative binomial regression was used to investigate associations between the number of MBs (dependent variable) and different clinical and imaging variables (independent variables) to account for the nonnormal distribution of MBs with an overrepresentation of zero values. Analyses were executed for both sequences separately. In a second model, the negative binomial regression analysis was adjusted for age and sex. Negative binomial regression data are represented as negative binomial regression

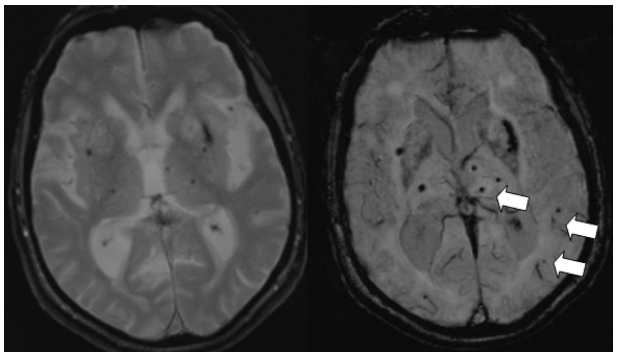

Figure 1. Gradient-recalled echo imaging (GRE, left) and susceptibility-weighted imaging (SWI, right) images of the same 82-year-old male Alzheimer disease patient, showing more lesions suggestive of microbleeds (arrows) and lesions with enhanced conspicuity on the SWI image compared with the conventional GRE image.

coefficients and their 95% CIs. These coefficients are multiplicative effect estimates of the variable of interest per unit increase. Statistical significance was set at $P<0.05$.

Results

MB Detection

The interrater agreement for the detection of MBs was excellent on both modalities, which is reflected by weighted Cohen's kappas for the 3 observers of at least 0.82 for MBs on GRE and of 0.87 on SWI. Intrarater agreement was also excellent, with weighted Cohen's kappa of 0.83 for GRE and of 0.86 for SWI.

In 32 (23%) patients, 1 or more MBs were found on conventional GRE imaging. On SWI, at least 1 MB was detected in 56 (40%) patients. A total of 219 MBs and 284 MBs were detected on GRE and SWI, respectively. In the groups with MBs, the median MB count was 1 (range, 1 to 144) on GRE and 2 (range, 1 to 129) on SWI (Wilcoxon signed-rank test $P<0.001$). In 43 patients, more MBs were detected on SWI than on GRE (Figure 1), equal numbers of MBs were detected in 90 patients, and in 8 patients more MBs were detected on GRE (Figure 2) than on SWI. The overall increase in the number of MBs on SWI was equally distributed among all lobes and nonlobar regions (data not shown).

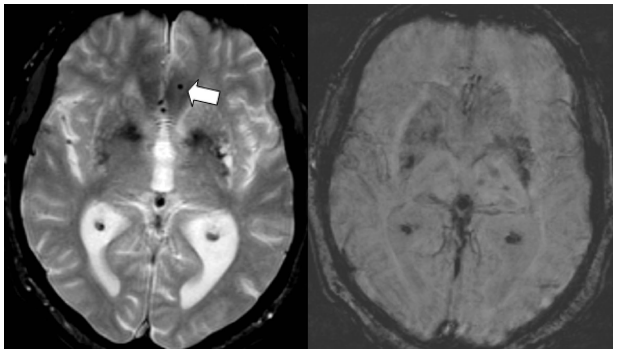

Figure 2. Gradient-recalled echo imaging (GRE, left) and susceptibility-weighted imaging (SWI, right) images of the same 77-year-old male patient with mild cognitive impairment, with 1 hypointense lesion in the left frontal lobe that was counted as a microbleed on GRE that appeared to be a vessel on SWI.

Multiple, strictly lobar MBs were detected in 6% of patients on GRE and in 14% on SWI ($P<0.01$).

Demographic, Clinical, Laboratory, and Radiologic Associations

We assessed the univariate associations of MB prevalence for both sequences with patient demographic, clinical, laboratory, and radiologic characteristics (Table 1). On GRE, age, sex, and diagnosis were not associated with MB prevalence. Regarding medical history, only diabetes mellitus was found to be less frequent in patients with MBs ($P=0.04$). MB presence on GRE was not associated with statin, anticoagulant, platelet inhibitor, or alcohol use; smoking status; Mini-Mental State Examination score; or apolipoprotein E status. Regarding other MRI characteristics, only lacunar infarcts were more frequent in patients with MBs than in patients without MBs on GRE ($P=0.002$).

On SWI, age was associated with the presence of MBs ($P<0.001$). In agreement with GRE, diagnosis and sex were not associated with MB prevalence on SWI. Medical histories were similar for patients with and without MBs, except for hypercholesterolemia, which was more frequent among patients with MBs on SWI. In contrast to GRE, there was no difference in the prevalence of diabetes according to the presence of MBs detected on SWI. Groups did not differ regarding statin or anticoagulant use; antiplatelet use, however, was more frequent in the group with MBs ($P<0.05$). Similar to GRE, Mini-Mental State Examination score and apolipoprotein E status were not associated with MB presence. In agreement with GRE, lacunar infarcts were more frequent in patients with MBs ($P<0.001$), but there were no associations with WMHs or large-vessel infarcts. Afterward, we restricted the analyses of MB prevalence to the 49 AD patients only. In contrast to the total population, age was significantly higher in AD patients with MBs on both sequences. Furthermore, no differences in clinical or laboratory variables in AD patients with and without MBs were found on any sequence. Similar to the total population, of the MRI characteristics, the presence of lacunes was associated with MB prevalence on both sequences.

Eighty-one patients had no MBs on both sequences. Of the 60 patients who presented with at least 1 MB on either sequence, 28 patients had MBs on both sequences. Another large subgroup of 28 patients had MBs on SWI not detected by GRE, that is, the patients were identified by the higher sensitivity of SWI. Only 4 patients were MB-positive on GRE only. Analyses of these subgroups compared with patients without MBs and with patients with MBs on both sequences can be found online (online-only Data Supplement).

In a subsequent analysis, we used negative binomial regression to study relations between the number of MBs and the aforementioned parameters (Table 2). On GRE, the following univariate associations were found: higher MB numbers were associated with older age ($P=0.004$), sex ($P=0.02$), the absence of diabetes mellitus ($P<0.001$), the absence of hypercholesterolemia ($P=0.03$), moderate to severe WMHs ($P=0.02$), and the presence of lacunar infarcts ($P=0.01$). When we entered age and sex as covariates in the

Table 1. Characteristics of Patients Without and With MBs on Both Sequences

Variables	No MBs on GRE, n=109	MBs on GRE, n=32	No MBs on SWI, n=85	MBs on SWI, n=56
Demographic				
Age, mean±SD, y	62±9	65±10	60±8	65±9†
Male sex, No.	61 (56%)	20 (63%)	47 (55%)	34 (61%)
Diagnosis				
SMC	16 (85%)	3 (15%)	14 (70%)	6 (30%)
MCI	11 (69%)	5 (31%)	9 (56%)	7 (44%)
AD	39 (80%)	10 (20%)	30 (61%)	19 (39%)
Other dementia	17 (94%)	1 (6%)	11 (61%)	7 (39%)
Other disease	25 (66%)	13 (34%)	21 (55%)	17 (45%)
Clinical				
Hypertension	22 (20%)	3 (9%)	16 (19%)	9 (16%)
Diabetes mellitus	13 (12%)	0 (0%)*	10 (12%)	3 (5%)
Hypercholesterolemia	14 (13%)	4 (13%)	7 (8%)	11 (20%)*
Current smoking	22 (22%)	5 (18%)	17 (22%)	10 (20%)
Alcohol >2/day	11 (11%)	4 (14%)	8 (10%)	7 (14%)
Statin use	7 (11%)	8 (9%)	7 (8%)	8 (14%)
Antiplatelet use	15 (14%)	5 (16%)	8 (9%)	12 (21%)*
Anticoagulant use	1 (2%)	2 (3%)	1 (1%)	2 (4%)
Systolic blood pressure, mm Hg	139±17	143±14	138±8	143±14
Diastolic blood pressure, mm Hg	85±9	86±8	85±9	86±10
MMSE score	25±5	25±4	25±5	25±4
Laboratory				
Apolipoprotein E				
Carrier ε2 allele	9 (11%)	3 (13%)	5 (7%)	7 (17%)
Carrier ε4 allele	37 (43%)	10 (42%)	32 (47%)	15 (36%)
Homozygous ε4	6 (7%)	2 (8%)	5 (7%)	3 (7%)
MRI				
MB No.	0	1 (1–144)	0	2 (1–129)
WMH score >1	19 (17%)	8 (25%)	12 (14%)	15 (27%)
Presence of lacunes	5 (5%)	7 (22%)†	1 (1%)	11 (20%)†

Data are represented as No. of patients with the variable present, No. (%), mean±SD, and for no. of MBs, as the median (range). Only incomplete data were available for smoking (130/141), alcohol use (129/141), and apolipoprotein E status (110/141). WMH score was assessed by using the Fazekas visual rating scale.

MB indicates microbleed; GRE, gradient-recalled echo imaging; SWI, susceptibility-weighted imaging; SMC, patients with subjective memory complaints; MCI, mild cognitive impairment; AD, Alzheimer disease; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; and WMH, white-matter hyperintensity.

*$P<0.05$, †$P<0.01$ (comparisons within sequence).

negative binomial regression model, only age and sex remained independently associated with MB number on GRE.

On SWI, higher MB numbers were also univariately associated with older age ($P=0.001$), sex ($P=0.01$), moderate to severe WMHs ($P=0.02$), the presence of lacunar infarcts ($P=0.004$), and, in addition to GRE, current smoking ($P=0.02$). After adjustment for age and sex, comparable to GRE, only age and sex remained independently associated with MB number on SWI. When we restricted these analyses to AD patients, the model could not be used owing to the small sample size.

Discussion

We confirmed that SWI is more sensitive for the detection of MBs in terms of overall prevalence and number, compared with conventional GRE. The assessment of MBs was accurate and reproducible, with excellent interrater and intrarater agreements. On SWI, the prevalence of MBs almost doubled and MB numbers per scan were higher, without any anatomic preference. As a result, probable CAA was seemingly more frequently detected on SWI. However, this gain in detection on SWI did not result in substantially improved relations between MBs and clinical characteristics, vascular risk factors, or other MRI expressions of small-vessel disease (that is, WMHs and lacunar infarcts), suggesting that even with the conventional, less-sensitive way of visualizing MBs, most patients with clinically relevant MBs are captured.

In addition, since a growing number of studies suggest that the number of MBs may be more clinically relevant than the mere presence of MBs, we investigated the influence of MB counts on both sequences. We found that by looking at MB count instead of presence only, male sex became additionally associated with MBs. The small-vessel disease marker WMH became strongly related to MBs, after accounting for MB number. This effect of MB number is in line with the notion that MBs may serve as a marker for small-vessel disease severity. In addition, we found that GRE and SWI were largely in agreement on these significant associations with MB number, underlining their validity. Discrepancies were hypercholesterolemia, which was more prevalent in patients with MBs on SWI but had a negative association with MB number on GRE, without adjustment. In the absence of a "gold standard," these differences are difficult to interpret; hypercholesterolemia is a known vascular risk factor, although low cholesterol levels are associated with MBs as well.[36] Unfortunately, cholesterol levels were not assessed in our study. Nevertheless, lipid-lowering medication use could not explain these observations in our population, because this was not different between groups. Another surprising finding was that current smoking seemed to protect against MBs on SWI, a trend also found on GRE in our population. Although counterintuitive, we think this could still be a valid observation, as the negative association was observed on both sequences and moreover has been found in patients with cerebrovascular disease in a systematic review of 11 large studies.[5]

Only 8 patients had higher MB counts on GRE. On close examination of these MBs on both sequences, these MBs were either misclassified on GRE; for example a vessel, visible only on SWI, was identified as an MB (Figure 2) or was not identified on SWI, caused by various technical reasons. This indicates that both GRE and SWI may have some limitations regarding true MB assessment. The higher number of MBs on SWI did not result in an improvement of the clinical and radiologic associations compared with the associations found on GRE. One may argue that the addi-

Table 2. Associations Between MB No. and Baseline Characteristics

	MBs on GRE		MBs on SWI	
Variables	Unadjusted Regression Coefficient	Regression Coefficient Adjusted for Age and Sex	Unadjusted Regression Coefficient	Regression Coefficient Adjusted for Age and Sex
Age	1.06 (1.00–1.12)†	1.06 (1.00–1.12)*	1.06 (1.01–1.10)†	1.05 (1.02–1.09)†
Male sex	3.17 (1.19–8.45)*	3.06 (1.16–9.04)*	2.50 (1.24–5.03)†	2.25 (1.15–4.41)*
Diagnosis				
SMC	Referent	Referent	Referent	Referent
MCI	0.97 (0.20–4.80)	0.79 (0.17–3.55)	3.10 (0.48–5.54)	1.50 (0.45–4.93)
AD	2.72 (0.54–13.74)	2.06 (0.45–9.41)	3.17 (1.01–10.01)*	2.77 (0.93–8.21)
Other dementia	0.12 (0.012–1.27)	0.14 (0.012–1.48)	0.85 (0.27–2.69)	1.17 (0.39–3.56)
Other disease	1.05 (0.25–4.44)	1.26 (0.34–4.71)	1.54 (0.54–4.40)	1.98 (0.78–5.04)
Hypertension	0.43 (0.086–2.12)	0.56 (0.13–2.47)	0.72 (0.30–1.69)	0.85 (0.38–1.92)
Diabetes	…	…	0.52 (0.11–2.40)	0.48 (0.12–1.84)
Hypercholesterolemia	0.30 (0.10–0.88)*	0.43 (0.10–1.93)	1.06 (0.48–2.35)	1.14 (0.49–2.68)
Current smoking	0.39 (0.12–1.24)	0.50 (0.16–1.53)	0.42 (0.20–0.87)*	0.61 (0.27–1.36)
Alcohol >2/day	0.37 (0.12–1.10)	0.77 (0.17–3.47)	1.07 (0.42–2.70)	1.62 (0.65–4.02)
Systolic blood pressure	0.97 (0.94–1.01)	0.98 (0.95–1.01)	0.98 (0.95–1.02)	0.99 (0.96–1.02)
Diastolic blood pressure	0.98 (0.91–1.04)	0.98 (0.93–1.08)	1.00 (0.96–1.04)	1.02 (0.98–1.05)
MMSE	0.92 (0.82–1.02)	0.92 (0.83–1.03)	0.93 (0.85–1.02)	0.94 (0.86–1.03)
Apolipoprotein ε2	0.46 (0.12–1.72)	0.73 (0.18–2.96)	1.07 (0.37–3.06)	1.09 (0.45–2.65)
Apolipoprotein ε4	1.45 (0.33–6.44)	1.52 (0.43–5.40)	1.22 (0.42–3.6)	1.25 (0.47–3.34)
Double ε4	0.91 (0.17–4.82)	1.74 (0.32–9.38)	0.95 (0.29–3.12)	1.06 (0.31–3.67)
WMH score >1	4.13 (1.23–13.9)*	2.77 (0.79–9.74)	2.91 (1.20–7.03)*	2.14 (0.90–5.12)
Presence of lacunes	4.05 (1.38–11.86)†	2.28 (0.71–7.36)	3.30 (1.45–7.48)†	2.08 (0.99–4.35)

Data are represented as negative binomial regression coefficients and (95% CI). WMH score was assessed by using the Fazekas visual rating scale.

MB indicates microbleed; GRE, gradient-recalled echo imaging; SWI, susceptibility-weighted imaging; SMC, patients with subjective memory complaints; MCI, mild cognitive impairment; AD, Alzheimer disease; MMSE, Mini Mental State Examination; and WMH, white-matter hyperintensity.

*$P<0.05$.

†$P<0.01$.

tional lesions detected by SWI, probably smaller ones, may more frequently be artifacts. However, this is unlikely and not supported by a recent pathologic-radiologic correlation study, relating all MBs on SWI to various pathologic findings.[2] Furthermore, although the significance of MB size remains controversial,[6] it may be argued that larger MBs, readily detectable on GRE, serve as a small-vessel disease marker, whereas perhaps smaller lesions, visible on SWI only, do so but only to a lesser extent. In addition, MB number may be considered the "tip of the iceberg" for underlying vascular pathology. Possibly, SWI merely exposes a slightly larger tip of the iceberg already visualized on GRE. Alternatively, power issues, owing to the relatively low prevalence of MBs, modest differences in MB counts, and heterogeneity of our current population may have attenuated the differences in clinical and radiologic associations, despite our advanced statistical approach. In the literature on MBs, considerable attention has been paid to the variability in prevalence and number of MBs, depending on the MR sequence used. Despite the observed difference in prevalence and number of MBs, associations with most characteristics were comparable. Therefore, our results provide support for the notion that in terms of clinical associations, the relevance of MBs is much more robust than previously thought.

Among the strengths of the current study are the direct comparison performed by a single rater of the 2 sequences on the same 1.5-T Siemens MR system in the same patient at the same time. Therefore, true pathology underlying MB lesions may be considered constant. Furthermore, our associations of MBs with clinical and MRI characteristics were performed within the same patients and the same measurements. We used negative binomial regression, because it has been demonstrated to be especially suitable for lesion count data and to provide a statistically more powerful parametric approach; it also allows for adjustment of covariates.[37–39] Limitations of the current study are that our sample was heterogeneous, with relatively small subgroups, resulting in limited power and limited generalizability; thus, our findings may be largely hypothesis-generating. In addition, we did not use a validated MB rating scale. Our definitions of definite MBs and MB mimics, however, are equal to the Microbleed Anatomical Rating Scale, and our agreements were also excellent.[40] Apart from minor anatomic scoring differences, the most notable difference is that we did not assess possible

MBs in our current study. Nevertheless, the authors of the Microbleed Anatomical Rating Scale proposed that for reliability purposes only, definite MBs may be used, since possible MBs have moderate reliability, possible reflected by our excellent agreement.

Furthermore, owing to small differences in slice thickness between the sequences, this study was not able to assess whether the benefit in detection is exclusively due to the use of added phase information.[41] Another limitation is that owing to differences in coverage, we could not consider infratentorial MBs, which may have altered the relations we have described. For example, MBs in the brain stem are common in patients with chronic hypertension.[16,42] MBs in the cerebellum, however, have been associated with both CAA and hypertension.[43,44] Therefore, we were not able to predict to what extent our associations of supratentorial MBs only with risk factors are biased. The size of this bias, however, may be rather small, since in a previous study in AD patients with multiple MBs, infratentorial MBs accounted for only 2% of the total MB count.[25] Finally, several adverse outcomes associated with baseline MBs, for example, large intracerebral hemorrhages and subsequent cognitive impairment[45] and mortality,[21] could not be evaluated due to the cross-sectional design of our current study.

The benefit of SWI over GRE may differ, depending on the magnetic field strength used, as susceptibility is proportional to the square of the magnetic field strength.[6,11] Therefore, the expected gain in improved MB detection at higher magnetic field strengths in combination with SWI and follow-up of the aforementioned adverse possible clinical implications should be evaluated in further studies. Notably, the current definitions of possible and probable CAA may need to be reestablished according to these more sensitive techniques.[33]

In conclusion, on SWI, higher MB numbers were detected in more patients, irrespective of MB location. On both sequences, MB number contributed to clinical and radiologic associations. On SWI, the associations found on GRE were corroborated; however, the higher MB numbers found on SWI compared with GRE did not improve these associations. Therefore, previous clinical MB studies with GRE may still be valid. Although SWI may present a promising role in clinical practice by possibly offering earlier detection of patients with bleeding-prone small-vessel disease, the exact clinical relevance of improved MB detection needs to be determined.

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Disclosures

None.

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