Neuroradiology
https://doi.org/10.1007/s00234-025-03663-5

REVIEW

Characterizing iron rim lesions in multiple sclerosis: a biomarker for disease activity and progression: a systematic review and meta-analysis

Nogol Motamedgorji[1] · Ashkan Bahrami[2] · Hayder jasim Taher[3] · Ahmed Mohamedbaqer Easa[4] · Sadaf Salehi[1] · Armin Tafazolimoghadam[5] · Mahan Farzan[6,7] · Zohreh Sadeghi[8] · Saharnaz Mofidinaeini[5] · Ramtin Hajibeygi[5,9] · Yaser Khakpour[10] · Mobina Fathi[11] · Anahita Zoghi[12] · Long H. Tu[9]

Received: 14 February 2025 / Accepted: 22 May 2025

Abstract

Background Iron rim lesions (IRLs) have emerged as important biomarkers in multiple sclerosis (MS), indicating chronic active inflammation and neurodegeneration. The purpose of this systematic review and meta-analysis is to assess the prognostic value of IRLs in MS, their impact on clinical outcomes, and their relationship with therapeutic responses.

Methods A thorough search was conducted across PubMed, Scopus, Web of Science, and Google Scholar, covering studies published until June 10, 2024. The inclusion criteria included studies on MS patients who had IRLs detected using advanced MRI techniques, particularly susceptibility-weighted imaging (SWI). The meta-analysis included 13 studies and a total of 924 MS patients. The data on clinical outcomes (EDSS scores, relapse rates), brain volume, and white matter lesion (WML) burden were combined. For continuous variables, effect sizes were calculated using standardized mean differences (SMDs), and for binary outcomes, relative risks (RRs).

Results This meta-analysis indicated significant correlations between IRLs and poorer clinical outcomes. IRL-positive individuals had higher EDSS scores (SMD 0.77, 95% CI: 0.34–1.21, p = 0.000), indicating a more severe impairment. They also had a larger WML load (SMD 0.52, 95% CI: 0.01–1.03, p = 0.000) and a smaller brain volume (SMD -0.50, 95% CI -0.82 to -0.19, p = 0.015). The relapse rate ratio was 1.10 (95% CI 0.73–1.65, p = 0.499), indicating a trend toward more frequent relapses in IRL-positive patients, though not statistically significant. Treatment response to disease-modifying treatments (DMTs) was similar in IRL-positive and negative individuals (RR 0.97, 95% CI: 0.89–1.06, p = 0.424). However, IRL-positive patients who received high-dose DMTs (HDMT) had a trend toward better outcomes (RR 1.2, 95% CI 0.94–1.52, p = 0.424).

Conclusions IRLs are strongly linked to higher disease severity, lesion burden, and neurodegeneration in MS patients. These lesions should be considered in routine medical evaluations since they are reliable prognostic indicators. Early intervention with high-dose treatment might offer potential benefits for IRL-positive patients, but further research is needed to determine the long-term clinical implications.

Keywords Iron rim lesions · Paramagnetic rim lesions · Multiple Sclerosis · Neuroinflammation · High-dose therapy · Prognostic markers

Introduction

Multiple sclerosis (MS) is a demyelinating condition characterized by focal lesions of axonal damage and myelin loss in the white and gray matter of the brain and spinal cord [1–3]. Lesions in MS are either gadolinium contrast enhancing acute lesions due to disruption of brain-blood barrier (BBB), or non-enhancing chronic lesions which might be active or inactive lesions [4]. A subtype of chronic active lesions which represents up to 50% of all chronic

Extended author information available on the last page of the article

Published online: 21 July 2025

active lesions, possesses a slowly expanding, smoldering nature with an inactive, demyelinated center [5, 6]. The aggregation of macrophages and microglial laden with iron deposits in the periphery of these chronic lesions creates an appearance of a hypointense rim which can be visualized through a susceptibility-weighted MR imaging (SWI) [7]. The SWI MR imaging is a type of imaging which unlike T1 and T2-weighted MRI can show the sedimentation of iron in the structure of the brain and can be useful in differentiating the subtypes of MS based on lesions' activity [8, 9]. Moreover, many studies suggest that IRLs are limited to chronic active MS lesions and are absent in other demyelinating conditions that serve as differential diagnoses for MS, which can be highly useful in the initial diagnosis of MS [10, 11]. In recent years, the term 'paramagnetic rim lesions' (PRLs) has also been used to describe lesions with paramagnetic characteristics observed on SWI or QSM (quantitative susceptibility mapping) [12], and also were included as additions to the McDonald criteria in 2024 [13]. While conceptually overlapping with IRLs, PRLs highlight susceptibility-based imaging signatures. For consistency with the majority of included studies, we use the term IRLs throughout this review but note the evolving terminology.

In terms of prognosis, iron rim lesions (IRLs) are most prevalent in late relapsing remitting phases and early stages of secondary progressive MS; therefore, the presence of IRLs may be a marker of disease progression [14]. On closer inspection, IRLs are considered to be associated with more severe myelin damage, reduced remyelination and irreversible tissue damage, indicating a worse outcome [15, 16]. IRLs are shown to be related to a higher ventricular volume, greater lesion load, and lower white matter and basal ganglia size. This highlights IRLs role as a both diagnostic and prognostic imaging tool [17].

Treatment options for MS are very variable and there are several factors influencing the type of disease modifying therapies (DMT) a patient receives. Some of these DMTs (glatiramer acetate, interferon-beta, teriflunomide or dimethyl fumarate also known as the plateau DMTs) are proven to have a safer profile but lower efficacy. Other DMTs known as "highly effective DMT" (H-DMT) are more effective in reducing lesion formation and recurrence rates, though they carry a higher risk of severe side effects like progressive multifocal leukoencephalopathy (PML) [18–20]. There is great controversy regarding the choice of DMT in different patients. Some experts prefer an escalation therapy, in which they commence the safest DMTs and if needed, escalate to higher efficacy medicines. Some expert value the prompt use of high efficacy DMT at onset of the disease [21]. The selection of DMT is largely based on the patient's prognostic factors, with poorer prognosis indicating the need for a more effective treatment [22]. The presence and number of IRLs are strongly associated with long-term clinical disability and worse scores on Expanded Disability Status Scale (EDSS) or Age-related Multiple Sclerosis Severity Score (ARMSS) [15, 17, 23]. Therefore, their utility in choosing the optimum treatment and monitoring the response to treatment should be further explored.

Given that MS is a debilitating disease requiring lifelong monitoring, identifying radiographic findings that can guide us in selecting treatments before the clinical symptoms appear could be highly valuable. This systematic review aims to comprehensively evaluate previous studied about the role of newly emerged IRLs in diagnosis and prognosis of MS which could be helpful in guiding experts regarding the further monitoring and management of patients.

Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [24] criteria to ensure accuracy in methodology and transparency. The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study. The ethic code is: IR.SBMU.RETECH.REC.1403.643.

Search strategy

A thorough search was conducted across PubMed, Scopus, Web of Science, and Google Scholar to identify original studies reporting on IRLs in brain MRIs of MS patients up to June 10, 2024. The search focuses on studies involving patients diagnosed with MS or clinically isolated syndrome (CIS) based on the revised McDonald criteria [25]. These studies used SWI MRI or other advanced MRI modalities to evaluate IRLs. Higher EDSS scores, more frequent relapses, reduced brain volume, and increased lesion burden were among the outcomes of interest. Manual searches of reference lists from relevant studies were performed as well to find additional articles.

Literature screening

The initial search found 3562 articles. Two independent reviewers (S.S. and N.M) carried out a two-phase screening process. In the first phase, titles and abstracts were evaluated for relevance. In the second phase, full-text articles were assessed for eligibility. Disagreements were resolved

through thirds reviewer (M.F). Human clinical studies investigating brain MRI findings of IRLs in MS patients were used as inclusion criteria. Review articles, conference abstracts, letters to the editor, commentaries, animal studies, and non-English publications were all excluded from the analysis. Furthermore, studies on conditions unrelated to MS or lacking MRI-based assessments of IRLs were excluded. (Figs. 1 and 2) illustrates the screening process in detail, including the reasons for exclusion.

Data extraction and quality assessment

Data were extracted independently by two investigators using a predefined Microsoft Excel spreadsheet. The extracted data included study characteristics such as first author, publication year, study design, country, sample size, and follow-up duration; participant characteristics such as age, gender, disease duration, history of DMTs, relapses, and EDSS scores; and imaging findings such as MRI modality, presence of IRLs, number and volume of IRLs, number and volume of WMLs, and total brain volume. In cases where appropriate, the median and interquartile range (IQR) were transformed into the mean and standard deviation (SD) for consistency in statistical analysis.. Across the included studies, the definition of IRLs was broadly consistent, referring to chronic MS lesions with hypointense rims on susceptibility-based imaging (SWI or QSM), partially or fully encircling a FLAIR-hyperintense lesion and visible on at least two or three contiguous slices. However, no standardized quantitative threshold for rim thickness was applied, and minor differences in descriptive criteria (e.g., dot-like signals vs continuous rims, lesion size thresholds) were observed. Most studies used independent dual ratings or consensus assessments for identifying IRLs, with some reporting high inter-rater agreement (e.g., 98.7%). However, observer bias cannot be excluded, as not all studies detailed their rating procedures.

The QUADAS-2 tool was used to assess the quality of the included studies, which focused on four key domains: patient selection, index test, reference standard, and flow and timing. Bias and applicability concerns were ranked as

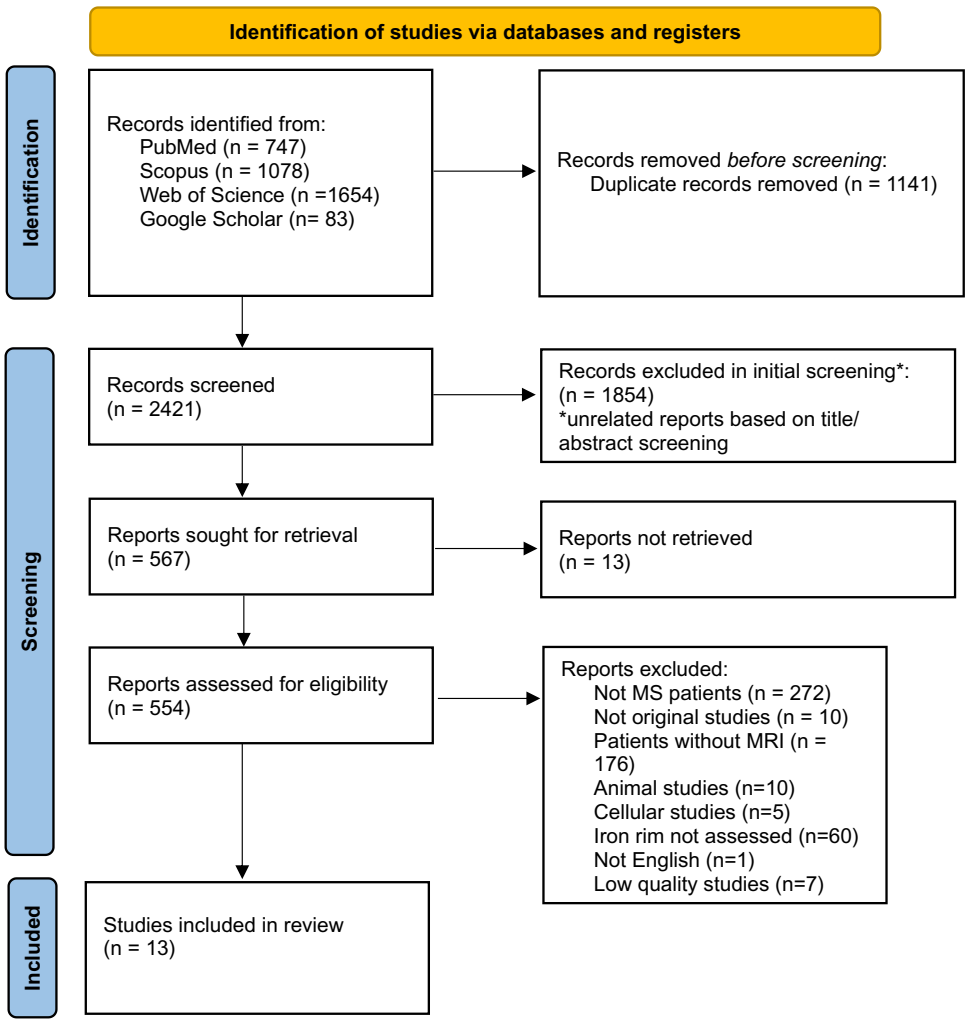

Fig. 1 Study flow diagram of included studies

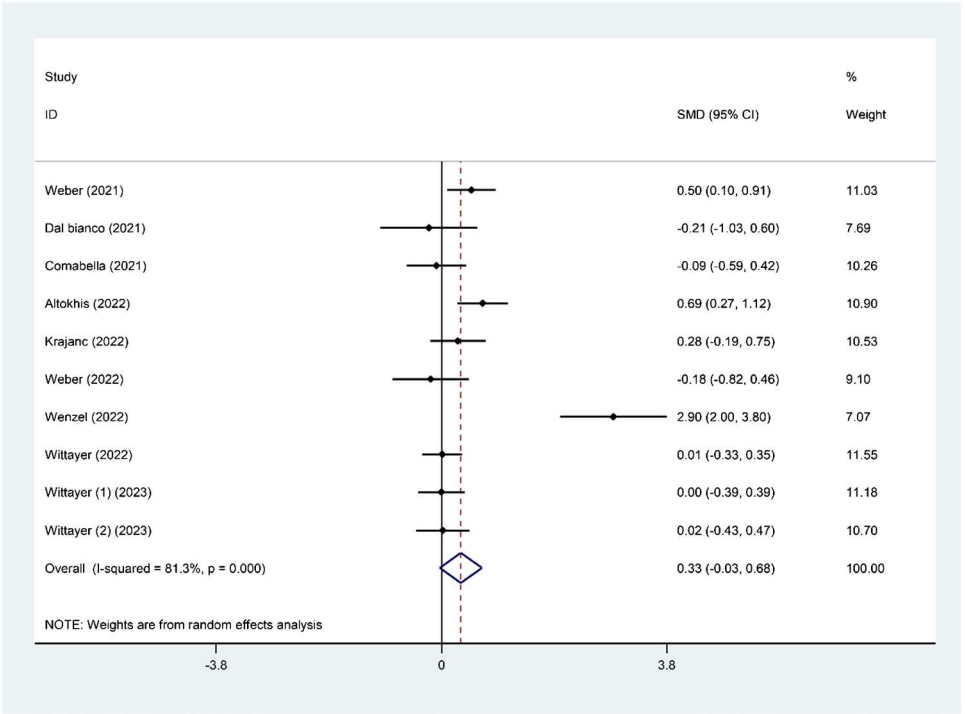

Fig. 2 Forest plot of the SMD of mean age in patients with IRLs in comparison to patients without IRLs. The weight of each paper on the meta-analysis is indicated by each parallelogram; the 95% CI is visualized by the interval within the boundaries. Literature is presented based on random effect model

"low," "high," or "unclear." The detailed results of the quality assessments are summarized in Table 3 Supplementary.

Data synthesis and analysis

A random-effects model was used in the meta-analysis to account for inter-study variability. SMDs were used to report effect sizes for continuous variables including EDSS scores and brain volume, as well as RRs for binary outcomes such relapse frequency. The I^2 statistic was used to assess heterogeneity, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high levels, respectively. To investigate sources of heterogeneity, subgroup analyses were conducted using study characteristics, patient demographics, and MRI modalities. The vast majority of studies used 3 T MRI; one study employed 7 T imaging [26], which may offer higher lesion resolution. Also, differences in MRI sequences were considered in the qualitative synthesis and discussed as a limitation. The publication bias was evaluated using funnel plots and Egger's test. Statistical analyses were carried out using STATA (Version 15).

Results

Study selection and characteristics

Initially, 3562 articles were obtained from searching databases including PubMed, Scopus, and Web of Science. 2995 records were excluded based on the title and abstract screening or being duplicates before assessing the full text. 303 out of 567 studies were filtered after elimination of non-English articles, reviews, non-available abstracts, and irrelevant to the main subject. The full texts of the 264 remaining articles were fully assessed, and 196 more studies were excluded due to unclear or insufficient data (n = 189) and low quality (n = 7). After full-text screening of the remaining articles, 13 articles were eligible and included in the meta-analysis (Fig. 1)(Table 1).

Adhering to PRISMA standards and conventions of meta-analysis [24], 924 patients were studied among the selected studies included 924 MS cases. From these, 494 showed iron rim lesions either in 3 T or 7 T SWI sequences of their brain MRI and 425 did not show any iron rim lesions. 5 patients initially revealed iron rim lesions which were temporary according to follow up imaging. Mean age of case group was 40.25 ± 9.98 years and the mean age of control group was 37.23 ± 11.40 years. According to, patients with iron rim exhibitions were significantly older than the other group (Fig. 2) Fig. 1.

Iron rim characteristics

PRLs are chronic active lesions seen in MS and are characterized as a rim of paramagnetic iron deposits surrounding a lesion frequently described in the context of IRLs. These lesions may be detected with advanced imaging techniques including SWI and QSM, which visualize iron deposition in the brain tissue. In general, PRLs appear as hyperintense lesions on FLAIR with hypointense rims surrounding them,

Table 1 Baseline characteristics of studies included in this meta-analysis

No	Year	Authors Name	Country	Study Design	Sample Size	Case Size	Follow up (month)
1	2022	Altokhis et al. [31]	UK	Retrospective study	91	42	108
2	2022	Krajnc et al. [18]	Austria	Retrospective study	75	47	NA
3	2021	Weber (1) et al. [32]	Germany	Cross-sectional investigation	102	49	12
4	2022	Weber (2) et al. [30]	Germany	Retrospective study	43	17	36
5	2021	Dal bianco et al. [26]	Austria	Cohot,) prospective observational design(	29	21	36
6	2021	Comabella et al. [49]	Spain	Prospective observational design	61	32	24
7	2022	Hu et al. [34]	China	Prospective study	42	34	NA
8	2023	Wang et al. [36]	China	Retrospectively analyze	99	73	NA
9	2022	Wenzel et al. [33]	Germany	Retrospective study	40	20	NA
10	2023	Kim et al. [35]	Italy	Cross-sectional investigation	30	14	101 ± 61.8
11	2022	Wittayer et al. [29]	Germany	Retrospective study	134	67	NA
12	2023	Wittayer (1) et al. [27]	Germany	Retrospective study	102	51	NA
13	2023	Wittayer (2) et al. [28]	Germany	Retrospective study	67	38	NA

suggesting chronic inflammation and neurodegeneration. Although this term IRLs is used interchangeably with PRLs in the literature, PRLs specifically signify the susceptibility-based imaging characteristics that allow for the detection of these lesions. Among those with iron rim lesion, mean lesion count was 2.73 ± 4.36 with a mean volume of 2.36 ± 4.99 ml for each patient. Wittayer et al.'s studies conducted in 2022 and early 2023, found that IRLs were predominantly located as follows: periventricular (49%), deep white matter (41%), and juxtacortical regions (10%) [27–29]. In Weber et al.'s study a tendency for developing in deep white matter followed by periventricular areas in both groups of temporary and permanent lesions was observed as well [30].

Meta-analysis

Iron rim lesions and disability status (EDSS Score) Most of the included studies used the EDSS as the primary measure of disability status. Patients with iron rim lesions had more severe disease, as indicated by a standard mean difference (SMD) of 0.77 in EDSS scores between the two groups (95% CI 0.34–1.21, I^2 = 87.3%) and P. value of 0.000 (Fig. 3)(Table 2).

Iron rim lesion and disease modifying therapy (DMT) The relative risk (RR) of DMT efficacy in patients with positive iron rim lesions (IRL +) compared with those without IRL (IRL-) was calculated to be 0.97 (95% CI, 0.89–1.06; I^2 = 0.0%) with a P. value of 0.481. These findings suggest a slightly better response in IRL- than in IRL + patients, although this difference is not statistically significant, indicating comparable efficacy of DMT between the two groups (Fig. 4).

Iron rim lesion and high-dose DMT (HDMT) For patients receiving HDMT, those with IRL showed a more favorable response compared with IRL- patients, with an RR of 1.2 (95% CI, 0.94–1.52; I^2 = 0.0) and a P. value of 0.424. While not statistically significant, this trend suggests that the presence of IRLs may influence the efficacy of second-line, intensive therapies such as HDMT and potentially reflects a distinct pathological response to treatment (Fig. 5).

Comparative analysis of DMT and HDMT outcomes in IRL + and IRL − patients When comparing DMT and HDMT outcomes in IRL + and IRL- populations, the RR for DMT in IRL + patients was less than 1, indicating that these patients were generally less responsive to first-line therapies compared with IRL- subjects. Conversely, the RR for HDMT in IRL + patients was greater than 1, emphasizing the greater dependence and efficacy of high-dose second-line interventions in this subgroup. This pattern suggests that IRL + patients may show a lower response to initial DMT regimens and require escalation to more intensive therapies such as HDMT. The differential response highlights the potential importance of IRL status in guiding treatment decisions and adjusting treatment strategies in the management of MS.

Relapsing rates and iron rim lesions Relapse rates were directly proportional to the presence of Iron Rims. According to our analysis, we found a significant association between the presence of IRLs and the relapse rate in patients

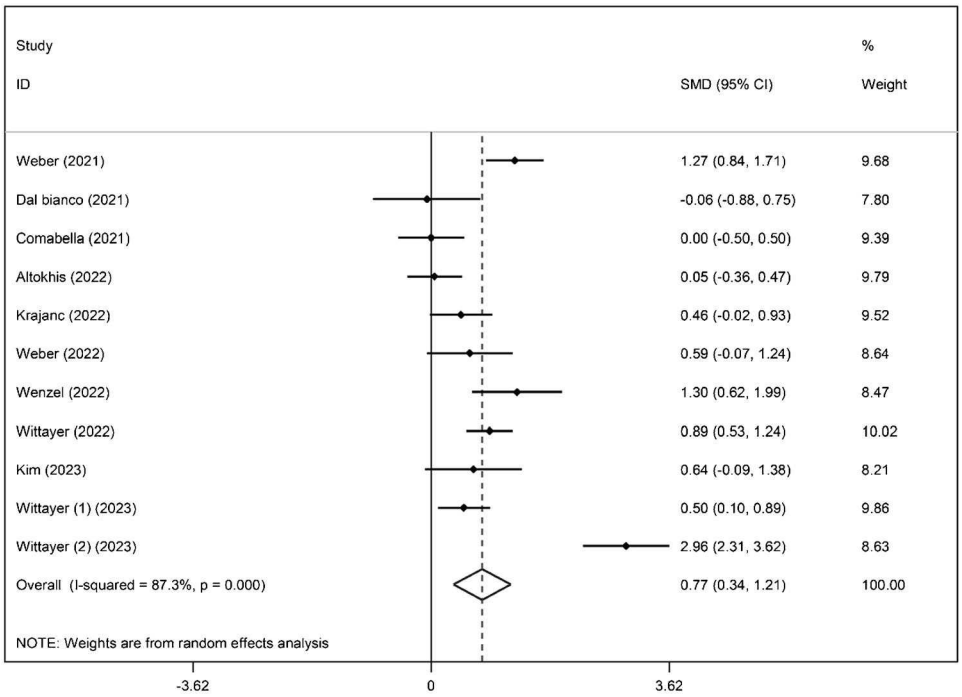

Fig. 3 Forest plot of the SMD of baseline EDSS in patients with IRLs in comparison to patients without IRLs. The weight of each paper on the meta-analysis is indicated by each parallelogram; the 95% CI is visualized by the interval within the boundaries. Literature is presented based on random effect model

Table 2 Summary of statistical analysis of included studies

	Number of Studies	RR	SMD	95% CI	I^2 (%)	P—Value
Mean age	10		0.33	−0.33, 0.68	81.3%	0.000
DMT Ratio	8	0.97		0.89, 1.06	0.0%	0.481
HDMT Ratio	7	1.20		0.94, 1.52	0.0%	0.424
Relapsing ratio	4	1.10		0.73, 1.65	0.0%	0.499
WML	7		0.52	0.01, 1.03	84.5%	0.000
Brain Volume	7		−0.50	−0.82, −0.19	62%	0.015
Baseline EDSS	11		0.77	0.34, 1.21	87.3%	0.000

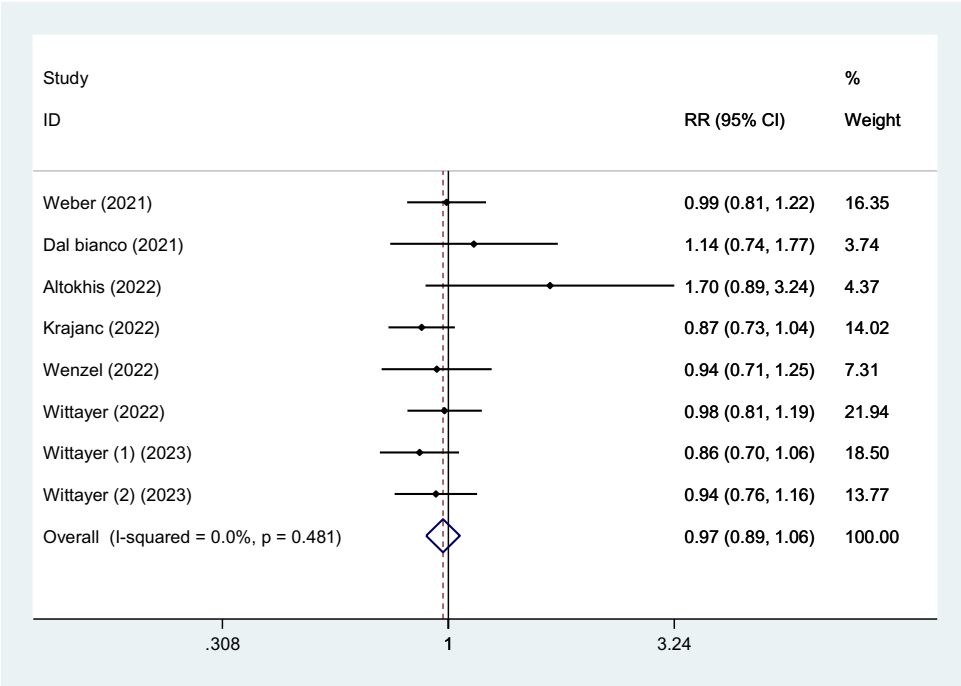

Fig. 4 Forest plot of the RR of DMT in patients with IRLs in comparison to patients without IRLs. The weight of each paper on the meta-analysis is indicated by each parallelogram; the 95% CI is visualized by the interval within the boundaries. Literature is presented based on random effect model

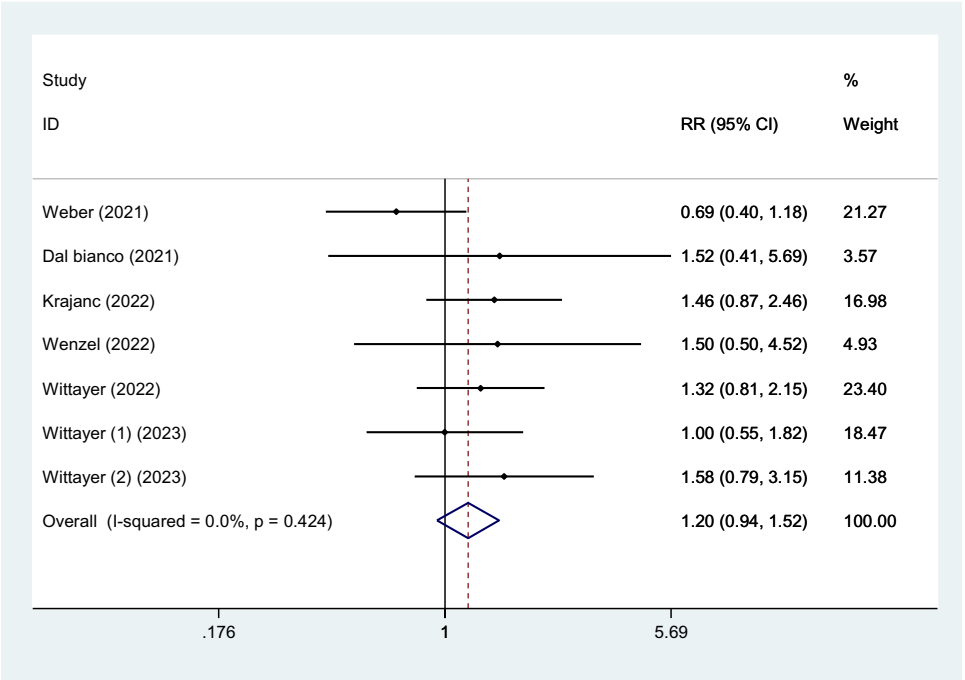

Fig. 5 Forest plot of the RR of HDMT in patients with IRLs in comparison to patients without IRLs. The weight of each paper on the meta-analysis is indicated by each parallelogram; the 95% CI is visualized by the interval within the boundaries. Literature is presented based on random effect model

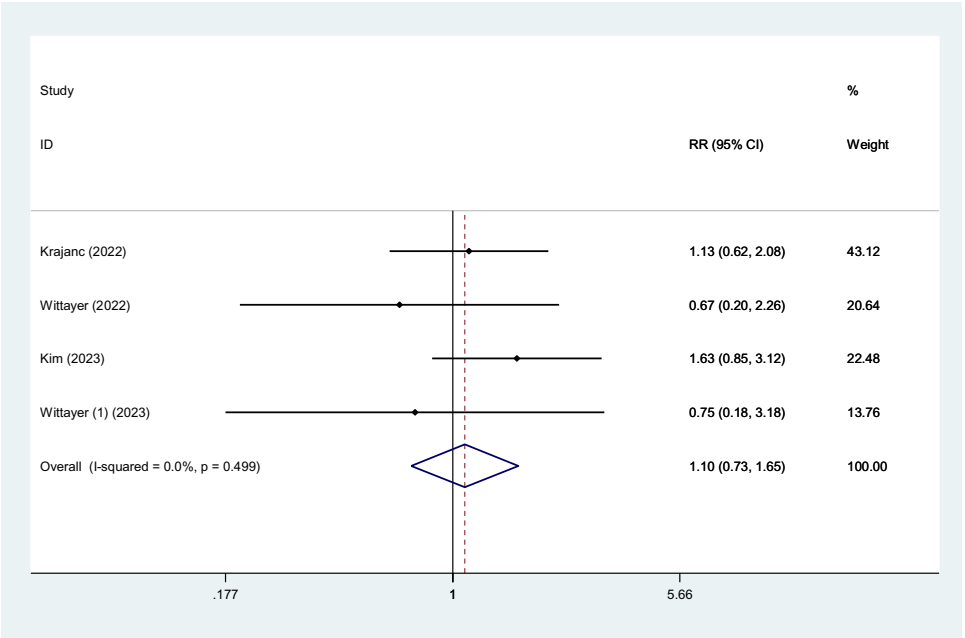

Fig. 6 Forest plot of the RR of relapsing disease in patients with IRLs in comparison to patients without IRLs. The weight of each paper on the meta-analysis is indicated by each parallelogram; the 95% CI is visualized by the interval within the boundaries. Literature is presented based on random effect model

with IRL of 1.10 (95% CI, 0.73–1.65; $I^2 = 0.0\%$) and a P. value of 0.499. This finding highlights the potential of IR as a predictive marker of disease progression (Fig. 6).

White matter lesions (WML) The SMD for WML was significantly higher in patients with IRL compared with those without IRL, with a SMD of 0.52 (95% CI, 0.01–1.03; $I^2 = 84.5\%$) and a P. value of 0.00 (Fig. 7).This finding suggests that patients with IRL present a significantly higher burden of WML, which could be related to the progressive pathology observed in these individuals. Furthermore, an inverse relationship was observed between WML burden and gray matter volume, suggesting that as WML increases, gray matter in the brains of IRL + patients decreases, potentially reflecting a more extensive neurodegenerative process.

Brain volume Analysis of brain volume revealed a significant reduction in patients with IRLs compared with those

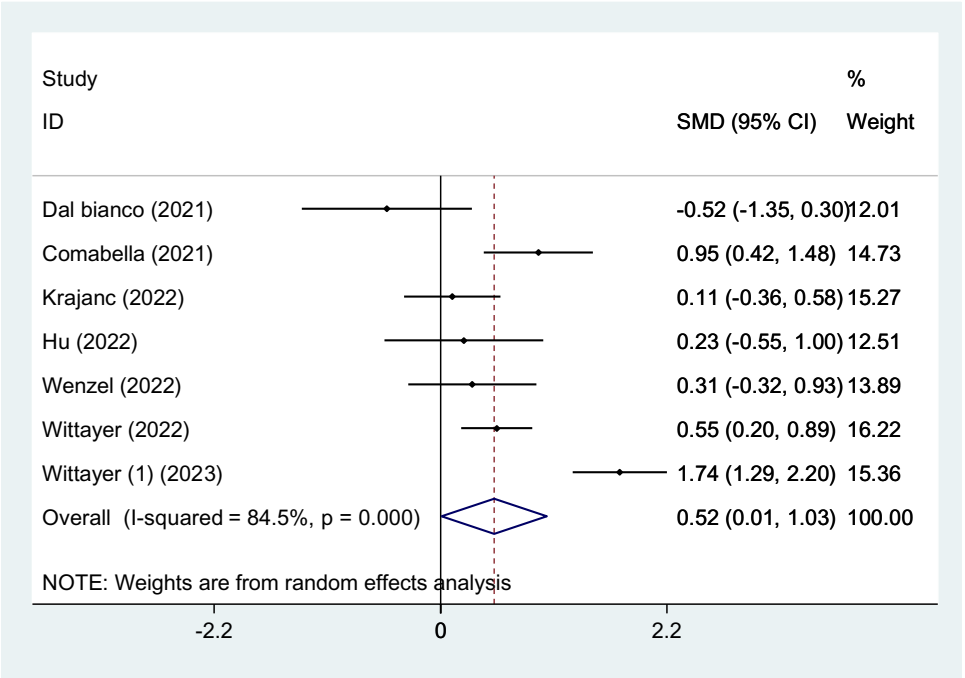

Fig. 7 Forest plot of the Standard Mean Difference (SMD) of white matter lesions (WMLs) in patients with IRLs in comparison to patients without IRLs. The weight of each paper on the meta-analysis is indicated by each parallelogram; the 95% CI is visualized by the interval within the boundaries. Literature is presented based on random effect model

without IRLs, with a SMD of −0.50 (95% CI, −0.82 to −0.19) and a P. value of 0.0015 (Fig. 8). This significant reduction in brain volume underscores the pathological impact of IRLs on overall brain integrity.

Sensitivity analysis The sensitivity analysis results demonstrated that any individual study or cluster of studies with shared characteristics had minimal influence on the effect size and its corresponding 95% confidence intervals (CI), indicating robustness in the findings. Sensitivity analysis rejected the null hypothesis of a single study or any cluster of studies with statistical outlier characteristics. Overall, all studies had minimal effect on effect size and 95% CI, confirming the robustness of the findings overall (Fig. 9).

Publication bias Figure 10 shows interpretation of Begg's funnel plot (P =0.764) and Egger test (P =0.520) shows

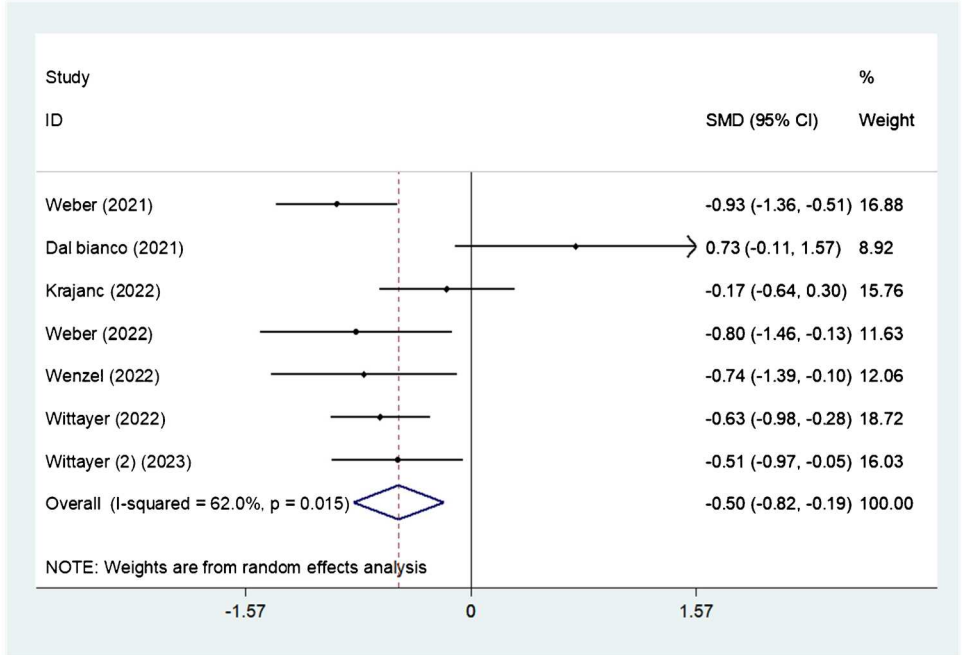

Fig. 8 Forest plot of the SMD of brain volume in patients with IRLs in comparison to patients without IRLs. The weight of each paper on the meta-analysis is indicated by each parallelogram; the 95% CI is visualized by the interval within the boundaries. Literature is presented based on random effect model

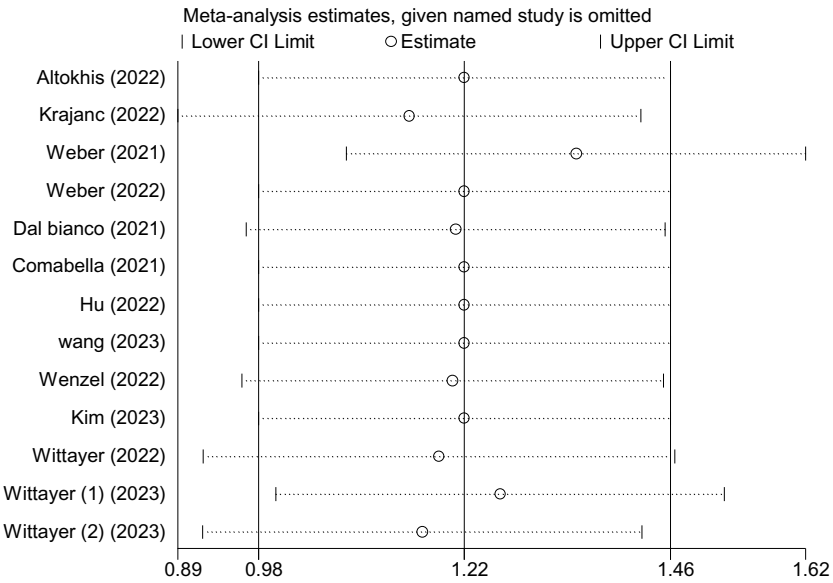

Fig. 9 Sensitivity analysis of the included studies in the prevalence analysis

Fig. 10 Begg and Egger's publication bias

```
Begg's Test

  adj. Kendall's Score (P-Q) =       3
        Std. Dev. of Score =    6.66
        Number of Studies =       7
                        z  =    0.45
                  Pr > |z| =   0.652
                        z  =    0.30 (continuity corrected)
                  Pr > |z| =   0.764 (continuity corrected)
```

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.9174203	.4589816	2.00	0.102	-.2624295	2.09727
bias	.9842221	1.422599	0.69	0.520	-2.672686	4.64113

no publication bias in the included studies. Therefore, it is understandable that reports have been published with both positive and negative outcomes (Figs. 10 and 11).

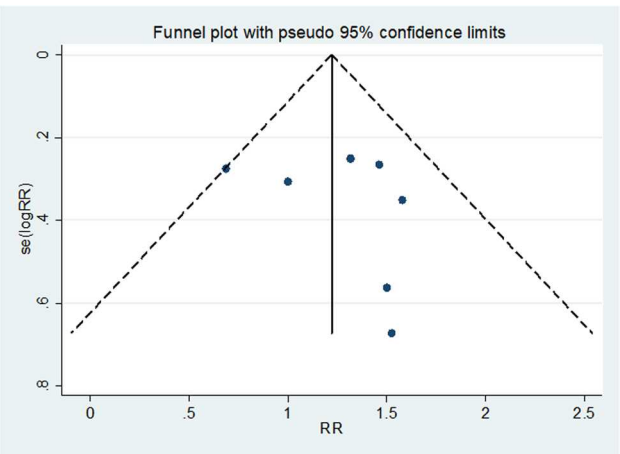

Fig. 11 Funnel plot of the publication bias

Systematic review

Relationship between IRL-positive patients and relapsing time and EDSS score Higher EDSS scores and longer disease duration are associated with IRLs. Altokhis et al. reported a mean EDSS (ARMSS) of 6.7 in IRLs + patients compared to 5.0 in IRLs- patients [31], with a median disease duration of 8 years versus 4 years [18]. While the differences in relapse frequency associated with EDSS were not significant, IRLs + patients were slightly more likely to have severe relapses (40.4% versus 35.7%) [18]. Weber et al. (2022) found that IRLs + patients had a higher baseline EDSS of 3.0 versus 1.0 in IRLs- patients ($p < 0.001$) and a longer, although not statistically significant, disease duration (8.58 versus 3.48 years) [32]. Dal-Bianco et al. revealed a consistent number of relapses (median 0) in both IRLs + and IRLs- groups [26], but Wenzel et al. found that IRLs + patients had a higher EDSS of 3.0 versus 1.3 ($p = 0.011$) [33], also Wittayer et al. in 2023, observed that EDSS scores

were significantly higher in IRLs +patients (2.5 versus 1.75, $p = 0.001$) [27] also were significantly higher through another study by Wittayer et al. (2.25 versus 1, $p < 0.001$) [28]. Advanced diffusion MRI measures, including MK, were associated with higher EDSS scores in IRLs +patients [34]. Overall, EDSS consistently showed more severe disease progression in IRLs +patients, despite variations in relapse frequency across studies.

Relationship between IRL-positive patients and disease-modifying therapies (DMT) MS patients with IRLs are more likely to be receiving DMTs, indicating rapid disease progression. Altokhis et al. found that 38% of IRLs +patients received DMT, compared to 22% of IRLs- patients, with an average DMT duration of 22.2 months [31]. Krajnc et al. discovered that 80.9% of IRLs +patients received DMT, with 57.4% receiving HDMT and 23.4% receiving M-DMT, compared to 60.7% of IRLs- patients, 39.3% receiving HDMT [18]. Weber et al. revealed no significant difference in overall DMT use (79% in IRL +patients vs. 80% in IRL- patients, $p = 1.0$), but persistent IRLs were associated with disease progression and treatment change (42%) [32].

According to Dal-Bianco et al., 48.3% of IRLs- patients were treated with first-line DMTs, while 34.5% of IRLs +patients received second-line DMTs [26]. IRLs +patients had larger lesion volumes (422.6 mm3 vs. 244.14 mm3, $p < 0.001$) compared to IRLs- patients [34], despite similar rates of DMT use (80% vs. 85%, $p = 1.0$) [33]. DMTs have shown limited efficacy in controlling disease progression in IRLs +patients, with higher lesion volumes and disability despite comparable rates of use[27, 28, 34]. These findings highlight the challenges of managing MS progression in IRLs +patients.

Relationship between IRL-positive patients and HDMT (Highly Effective DMT) MS patients with IRLs are more likely to require HDMTs, as shown by Altokhis et al., where 38% of IRLs +patients received HDMT, mainly natalizumab, with a median treatment duration of 16.8 months [31]. Krajnc et al. found that 57.4% of IRLs +patients received HDMT compared to 39.3% of IRLs- patients ($p = 0.024$) [18]. In Weber et al., 37% of IRLs +patients received HDMT compared to 24% of IRLs- patients, although this difference was not statistically significant ($p = 0.34$) [32]. Despite HDMT use, IRLs +patients had higher lesion volume (T1-LV and T2-LV), indicating active disease progression[30]. Dal-Bianco et al. (2021) found that 34.5% of IRLs +patients switched to second-line therapies such as natalizumab or fingolimod during follow-up [26]. Wenzel et al. reported a 30% increase in HDMT use among IRLs +patients compared to IRLs- ($p = 0.716$) [33], while Wittayer et al. noted that IRLs +patients were more likely to require HDMTs but still showed higher lesion volume and disability scores, even with intensive treatments (25.3% vs. 29.4% for IRLs-, $p = 0.657$) [27]. These findings suggest that IRLs are indicative of aggressive disease progression requiring repeated use of HDMT but with limited control over lesion growth and disability.

Relationship between RRMS and relapsing rates with IRL-positive patients Patients with RRMS and IRLs experience a higher disease burden, with IRLs often representing advanced stages of RRMS. Krajnc et al. found significant associations between the number of IRLs and disease duration (rs = 0.239, $p = 0.039$) and RRMS (70.2% of IRL +patients, $p = 0.128$) [18]. Weber et al. observed that 36 of 43 RRMS patients with persistent IRLs had larger lesion volumes [30]. Dal-Bianco et al. reported 17 of 21 (80.9%) RRMS in the IRLs +group [26]. Hu et al. emphasized that 12.16% of IRLs +patients, experienced RRMS [34]. Kim et al. confirmed the role of IRLs in increasing lesion burden, with 74% of IRLs +RRMS patients showing a mean lesion volume of 6.49 mL compared to smaller volumes in non-IRLs [35]. Wittayer et al. found 86.5% in RRMS patients with IRLs +had RRMS [29]. Similarly, 90.2% of patients with IRLs had RRMS, with significantly larger lesion volumes than those without IRLs (4.85 mL vs. 2.39 mL, $p < 0.001$) [27]. In summary, IRLs are associated with higher lesion burdens and disability, making them important markers of disease progression in RRMS patients.

Relationship between IRL-positive patients and white matter lesions (WML) IRLs are strongly associated with increased WML burden in terms of volume and tissue damage. Altokhis et al. reported that 9% of 1468 WMLs were IRLs, with IRLs +patients showing a larger WML volume (97,610 mm3) compared to IRLs- patients (37,279 mm3) [31]. Krajnc et al. observed that IRLs +patients had a higher median number of lesions (24 vs. 16, $p = 0.266$) [18]. Weber et al. found significantly lower NAWM volume in IRLs +patients (722.43 ml vs. 745.16 ml, $p = 0.04$) and higher T2 lesion volume (9.08 ml vs. 4.53 ml, $p < 0.05$) [32]. Persistent IRLs increased in size over six years, whereas non-persistent IRLs decreased [32]. Kim et al. noted a significantly higher number of WMLs in IRLs +patients (27.0 ±16.8) compared to IRLs- patients (8.6 ±10.8, $p = 0.001$) [35]. Wang et al. confirmed a strong correlation between WML volume and IRLs in RRMS patients (r = 0.45, $p = 0.003$) [36]. Hu et al. demonstrated severe tissue damage in IRLs +WMLs based on diffusion imaging measures such as MD and MK [34]. Wittayer et al. found more perilesional damage around IRLs, with higher ADC values in IRLs +WMLs (1.09×10^{-3} mm2/s) compared to non-persistent IRLs (1.04×10^{-3} mm2/s, $p = 0.007$) [27]. These findings highlight that

IRLs are a key factor in the progressive burden of WML and tissue damage in MS.

Relationship between IRL-positive patients and brain volume In MS patients, IRLs are strongly associated with accelerated brain atrophy and reduced brain volume. Krajnc et al. found that the mean brain volume for IRLs + patients was 1077.4 mL, compared to 1096.3 mL for IRLs- patients, but this difference was not statistically significant (p = 0.385) [18]. IRLs + patients had an even greater reduction in brain tissue volume in contrast to IRLs—patients, with total NAGM volume of 739.74 mL vs 790.89 mL, and with P. value = 0.002, and also and total NAWM volume of 722.43 mL vs 745.16 mL (p = 0.04) [32]. According to Dal-Bianco et al., IRLs + patients had a decrease in thalamus volume by 14.03 ml and 16.5 ml, respectively, p = 0.045, whereas thalamus volume decreased by a small volume in putamen three years later by 8.0 ml and 8.1 ml, p = 0.043 [26]. Wang et al. found that RRMS IRLs + patients had a lower total brain volume (765.98 ml) compared to healthy individuals (802.37 ml), p < 0.001 [36]. They also discovered a negative relationship between the caudate-putamen nucleus and total brain volume (r = −0.30, p = 0.006) [36]. IRLs + patients showed significant brain tissue loss, especially in critical regions such as the thalamus and putamen, highlighting the role of IRLs in structural degradation and MS progression (Figs. 12 and 13).

Relationship between IRL-positive patients and gray matter (GM) IRLs are associated with a significant reduction in GM volume, especially in deep gray matter (DGM). Krajnc et al. found no significant difference in total GM volume between IRLs + and IRLs- patients (666.5 mL vs 666.5 mL, p = 0.648) [18]. Weber et al. revelaed that IRLs + patients had lower NAGM volume than controls (739.74 mL vs. 790.89 mL, p = 0.002), as well as lower DGM volume (33.45 mL vs. 35.32 mL, p = 0.02) [18]. Dal-Bianco et al. discovered that IRLs + patients had a higher rate of thalamic volume loss after three years (0.29 mL vs 0.06 mL, p = 0.019) [26].

Wenzel et al. indicated that IRLs + patients have a lower DGM volume, with an average of 32.82 ml vs 34.83 ml (P < 0.05) [33]. Wang et al. found a significant decrease in mean thalamic volume from 10.23 mL in healthy controls to 8.86 mL milliliters (almost 2 ml lower) in IRLs + patients (p <

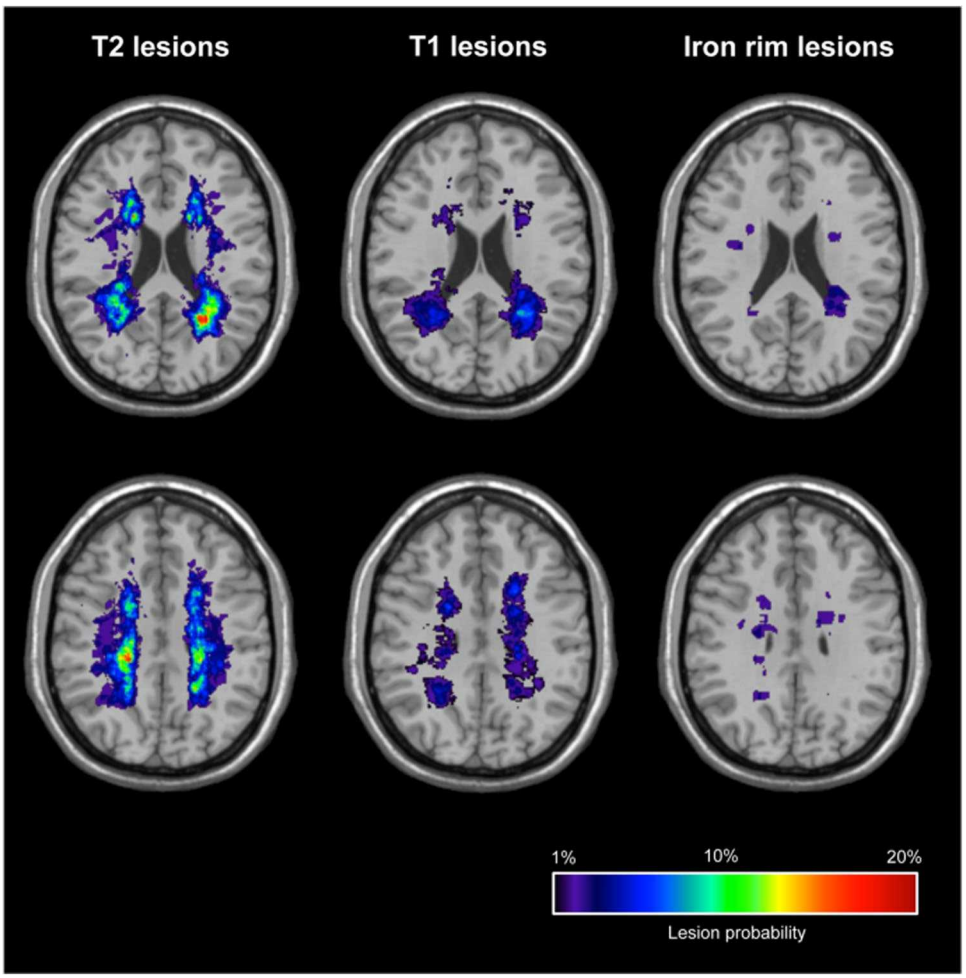

Fig. 12 Heat map representation of relative probabilities of T2-hyperintense, T1-hypointense, and iron rim lesions computed over all patients included in the study of Weber et al. superimposed on a MNI152 template [32]

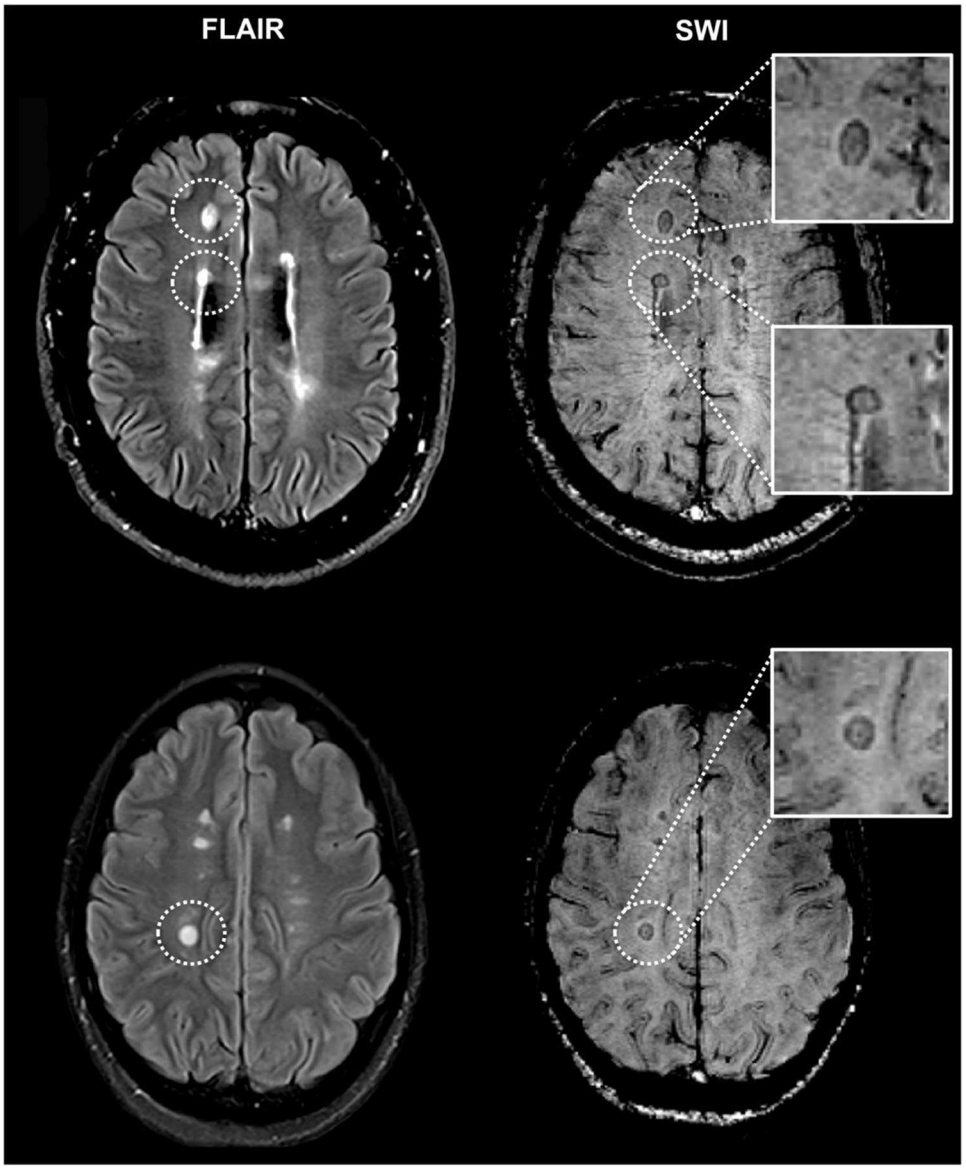

Fig. 13 Association of iron rim lesions with brain and cervical cord volume in relapsing multiple sclerosis [32]

0.001) [36]. Wittayer et al. found that IRLs + patients had a lower GM volume (765.62 mL vs. 780.93 mL, $p < 0.01$) and DGM volume (33.23 mL vs. 36.0 mL, $p < 0.05$) [28].

These findings confirm that GM atrophy is more prominent in IRLs + patients, especially in critical regions such as the thalamus and putamen, and emphasize the progressive nature of IRLs in MS-related brain damage.

Discussion

Our study found a strong correlation between IRLs and higher EDSS scores (SMD 0.77, $p = 0.000$), which indicates that patients with IRLs have a more advanced disease burden. These results are in line with those of Wang et al. [36], who found that patients with IRLs had significantly higher median EDSS scores (2.25; IQR 1.37–3.5) than those without IRLs (1.0; IQR 0.75–2.0), indicating a link between IRLs and more severe clinical disability. Moreover, Maggi et al. provided support for this idea by demonstrating that patients with ongoing IRLs had consistently higher EDSS scores throughout a 10-year follow-up period, indicating that IRLs may be indicators of progressive neuroinflammatory activity [37].

According to Altokhis et al. in 2022, EDSS scores were substantially higher in patients with four or more IRLs, reaching a median of 6.0 [31]. Our results are in line with this finding, which further demonstrates that the effect of IRL burden on disability is dose-dependent. The clinical utility of IRLs in predicting advanced disability was further highlighted by Wittayer et al., who revealed that patients with IRLs + had EDSS scores about 1.5 points higher than IRL-negative individuals [29].

Longitudinal studies provide more evidence that IRLs are useful as prognostic markers. Supporting the hypothesis that these lesions could be related to ongoing axonal damage and chronic neurodegeneration, Elliott et al. in year 2023, found that IRLs + patients had a 30% higher rate of EDSS progression than those without [38]. Absinta et al. also showed the correlation between EDSS scores, lesion volume, and rim persistence over multiple years, highlighting the association between paramagnetic rims and long-term disability [17].

The results of our meta-analysis indicated that patients with IRL + had different responses to treatment. Normal DMT efficacy was similar in the IRL + and IRL- groups (RR0.97, p = 0.424), but HDMT efficacy was better in the IRL + group (RR1.2, p = 0.424). Similarly, Pontillo et al. in 2023, found that intensive treatments like natalizumab and alemtuzumab were more effective against IRLs, but that IRLs were linked to resistance to first-line therapies [39]. 40% of IRLs were found to have remained or grown in size even after receiving standard treatments, according to the study in 2023 by Clarke et al., underscoring the necessity for individualized strategies for managing their specific pathology [40].

Targeting macrophage-mediated inflammation was suggested by Sandi et al. in the year 2021, considering macrophages are essential for maintaining the chronic activity of IRLs [41]. In a similar way, Wittayer et al. found that initial treatments for IRLs were ineffective for Approximately, 60% of patients, necessitating therapeutic escalation and the subsequent use of second-line therapies such as ocrelizumab [29]. While these findings indicate that HDMTs hold significance for IRL + MS management, the fact that lesions are still present after treatment implies the present methods remain suboptimal.

In line with Absinta et al. in 2021, our study demonstrates that paramagnetic rim lesions cannot be resolved well with conventional treatments, indicating that IRLs need more specialized interventions [42]. Lesion volumes in IRL + patients increased by 12% annually despite HDMT use, according to Altokhis et al., suggesting the need for more targeted, precise treatments to effectively slow disease progression [31]. Novel therapeutic approaches that target the microglial activation and iron dysregulation underlying IRLs have the potential to be enhanced by these findings.

Patients with IRL + had a higher risk of severe exacerbations, as shown by their relapse rate ratio of 1.10 (p = 0.499) [14]. Relapse rates were approximately 1.6 times higher among IRL + patients compared to IRL- patients, according to Kim et al. through 2023, providing confidence to this finding [35]. Reeves et al. in year 2023, found that patients with IRLs had more severe relapse episodes, with increased radial diffusivity and perilesional tissue damage, further associating IRLs to more severe relapses [43].

Another prominent feature associated with IRLs was neurodegeneration. Improving upon prior studies, Haider et al. concluded that IRLs drive progressive neurodegeneration by accelerating gray matter volume loss in conjunction with iron accumulation within lesion rims [44].

patients with IRL + had thinner mean cortical thickness (P < 0.001), higher mean GWR (P = 0.001), and lower brain structure volumes (cortex volume, P = 0.001; WM volume, P < 0.001; deep GM volume, P < 0.001) [45]. Similarly, due to the inflammatory and neurodegenerative effects of these lesions, Dal Bianco et al. revealed that DGM volumes were significantly lower in patients with IRLs compared to those without [26]. Together, these findings demonstrate that IRLs are central to both relapse dynamics and long-term neurodegeneration in MS.

Our analysis demonstrates that IRLs contribute to the development of advanced MS pathology by greatly increasing the burden of WMLs, brain atrophy, and DGM atrophy. Weber et al. found that patients with IRLs had a higher lesion load, especially in deep white matter and periventricular regions [32]. Our findings indicate that IRLs are associated with an increased WML burden (SMD 0.52, p = 0.000). Further evidence of the aggressive inflammatory profile was provided by Wittayer et al., who determined that WMLs containing IRLs had higher growth tendency than non-IRLs [27].

In terms of brain volume reduction, our study indicated a significant decrease in IRL-positive patients (SMD −0.50, p = 0.015). This finding is in accordance with what Altokhis et al. found: individuals with four or more IRLs had 30% faster brain atrophy than those without IRLs, which was associated with impaired motor and cognitive functions [31]. This was verified by Pontillo et al.in 2023, who discovered that lesions associated with IRL caused increase in subcortical atrophy and cortical thinning, with a focus on the thalamus and putamen [26, 32].

In particular, IRLs had a disproportionate impact on the thalamus and other DGM structures. According to Dal Bianco et al., there is a strong correlation between cognitive impairment and disease progression and the fact that IRL-positive patients revealed thalamic volume loss of up to approxiamatley15% compared to non-IRL patients [26]. Furthermore, it has been found by Rudko et al. through the year 2014, that QSM revealed increased iron accumulation in the thalamus of IRL-positive patients, which additionally correlates these lesions to severe neurodegeneration [46].

The crucial role of IRLs in increasing the load of WML, leading to regional and global brain atrophy, and targeting DGM structures is highlighted by these findings from our analysis and the literature taken together. The findings emphasize the need of including IRL evaluations in routine

clinical imaging in order to comprehend and lessen their impact on MS progression.

The implications of IRLs as imaging biomarkers for MS progression are further highlighted by our study. To help distinguish IRLs from other types of lesions, advanced imaging methods like quantitative susceptibility mapping (QSM) have demonstrated the ability to precisely assess iron deposition within lesion rims. An important tool for assessing lesion activity and chronic inflammation, QSM has been demonstrated by the Harada et al. in the year 2022, to reliably detect iron accumulation.

The R1 relaxometry was described by Pontillo et al. in 2021, as a means to evaluate myelin and iron alterations in areas adjacent to IRLs, which increases the diagnostic value of imaging biomarkers [47]. Patients with IRLs + exhibited more severe cognitive and motor impairments owing to deeper tissue damage compared to non-IRL lesions, according to the study by Rudko et al. using susceptibility-weighted imaging (SWI) [46].

According to Dal Bianco et al. IRL-associated lesions such as FLAIR Lesions contribute to the overall disease burden due to the fact their volumes are 2.78 times higher than non-IRL lesions [26]. In light of the interaction between inflammation and neurodegeneration induced by these lesions, due to the study in 2021 by Lou et al. discovered that perilesional cortical atrophy was 28% more severe in patients with IRL + [48]. Together, these imaging developments emphasize how important IRLs are for directing MS prognosis, diagnostics, and treatment strategies.

Limitations

This study has several limitations, including the heterogeneity of imaging techniques and diagnostic criteria across included studies, which may cause variability in the findings. The reliance on advanced imaging tools such as SWI and 7 T MRI limits its applicability to settings lacking such technology. A limitation of this meta-analysis is the minor variability in the operational definitions of IRLs across studies, particularly regarding rim thickness and imaging criteria. While core characteristics were consistent, future studies should work toward a consensus-based definition. Observer bias in IRL identification remains a concern. While many studies used independent raters or consensus protocols, some did not report their blinding or training procedure. Many studies have small sample sizes and are retrospective, reducing statistical power and potentially introducing bias. Furthermore, a lack of longitudinal data limits causality assessments between IRLs and disease progression, and inconsistencies in reporting treatment adherence and comorbidities may skew results. Assessing IRLs in initial MRIs and tracking them longitudinally could validate their use as prognostic markers, allowing for more effective monitoring of disease progression. Clinical trials investigating the early use of HDMTs in patients with poor prognostic factors (e.g., older age, male gender, multiple IRLs) could reveal benefits in terms of reducing EDSS progression and brain atrophy. Research into the role of iron metabolism and microglial activity in IRLs may lead to the development of targeted therapies to treat chronic inflammation and neurodegeneration. Large-scale, longitudinal studies are required to investigate the long-term evolution of IRLs and their impact on clinical outcomes. Combining SWI with other modalities, such as QSM and DTI, could improve IRL detection and prognosis. Differences in MRI sequences (SWI vs QSM) and magnetic field strengths may have affected IRL detection rates and lesion appearance. While most studies used 3 T SWI, the inclusion of one 7 T study introduces potential bias related to higher sensitivity. These suggestions aim to address the study's limitations and optimize the role of IRLs in MS management, thereby improving diagnostic accuracy and treatment outcomes.

Conclusion

As indicators of severe disease progression, neurodegeneration, and therapeutic outcomes, IRLs play a significant role in MS, according to this study. Brain atrophy, DGM, and the burden of white matter lesions were all considerably higher in IRL + patients than in IRL- ones. As shown by higher EDSS scores and increased relapse rates, their lesions exhibited more destruction and were associated with more severe clinical symptoms. The study demonstrates that IRL + lesions are pathologically aggressive, leading to inflammation and neurodegeneration and a worsening of disease outcomes.

It is difficult to manage IRL + patients because HDMTs are often required due to progressive disability and frequent relapses. Our findings indicate that HDMTs are more effective than standard treatments for IRL + patients, especially in preventing relapses and slowing the progression of EDSS. However, it is clear that more targeted treatments are needed to address the chronic inflammation and iron dysregulation linked to IRLs, since persistent lesion activity persists even when HDMTs are used.

Diagnostic precision and useful prognostic information could be enhanced by integrating IRL evaluations into standard MRI protocols. Their potential as prognostic indicators can be further confirmed with the use of longitudinal imaging to monitor the development of IRL in conjunction with clinical follow-up. Additionally, there are possibly novel approaches of reducing the impact of the disease and improve long-term results by continuing to investigate

the feasibility of starting HDMT early in high-risk IRL + patients. The specific challenges caused by IRLs in the management of MS need to be addressed by personalized therapeutic approaches, as this study illustrates.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00234-025-03663-5.

Acknowledgements The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation, and assistance throughout the study (Grant Number: 43013184) (IR.SBMU.RETECH.REC.1403.643). We also want to thank Dr. Paria Bolourinejad for her help.

Author contribution NM and AB wrote the main manuscript text. HJT prepared Figs. 1–3. AME, SS, AT, MF, ZS, SM, RH,YK, and MF contributed to data collection, analysis, and manuscript writing. AZ and LHT supervised the study and critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding None.

Data availability No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

References

1. Charcot J-M (2011) Leçons sur les maladies du système nerveux: faites à la Salpêtrière, vol 2. Cambridge University Press
2. Brück W et al (1995) Monocyte/macrophage differentiation in early multiple sclerosis lesions. Ann Neurol: Off J Am Neurol Assoc Child Neurol Soc 38(5):788–796
3. Frischer JM et al (2009) The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 132(5):1175–1189
4. Dal-Bianco A et al (2017) Slow expansion of multiple sclerosis iron rim lesions: pathology and 7 T magnetic resonance imaging. Acta Neuropathol 133(1):25–42
5. Kuhlmann T et al (2017) An updated histological classification system for multiple sclerosis lesions. Acta Neuropathol 133:13–24
6. Kaunzner UW et al (2019) Quantitative susceptibility mapping identifies inflammation in a subset of chronic multiple sclerosis lesions. Brain 142(1):133–145
7. Martire MS et al (2022) What is the potential of paramagnetic rim lesions as diagnostic indicators in multiple sclerosis? Expert Rev Neurother 22(10):829–837
8. Gillen KM et al (2021) QSM is an imaging biomarker for chronic glial activation in multiple sclerosis lesions. Ann Clin Trans Neurol 8(4):877–886
9. Haacke EM et al (2004) Susceptibility weighted imaging (SWI). Magn Reson Med: Off J Int Soc Magn Reson Med 52(3):612–618
10. Chawla S et al (2016) Iron and non-iron-related characteristics of multiple sclerosis and neuromyelitis optica lesions at 7T MRI. Am J Neuroradiol 37(7):1223–1230
11. Hosseini Z et al (2018) Morphology-specific discrimination between MS white matter lesions and benign white matter hyperintensities using ultra-high-field MRI. Am J Neuroradiol 39(8):1473–1479
12. Hemond CC et al (2024) Paramagnetic rim lesions are highly specific for multiple sclerosis in real-world data. medRxiv
13. Montalban X (2024) Revisions of the McDonald criteria. In: 40th Congress of the European committee for treatment and research in multiple sclerosis (ECTRIMS). 2024: Copenhagen, Denmark p. Scientific Session 1: New Diagnostic Criteria.
14. Absinta M, Dal-Bianco A (2021) Slowly expanding lesions are a marker of progressive MS–Yes. Mult Scler J 27(11):1679–1681
15. Absinta M et al (2016) Persistent 7-tesla phase rim predicts poor outcome in new multiple sclerosis patient lesions. J Clin Investig 126(7):2597–2609
16. Fischer MT et al (2013) Disease-specific molecular events in cortical multiple sclerosis lesions. Brain 136(6):1799–1815
17. Absinta M et al (2019) Association of chronic active multiple sclerosis lesions with disability in vivo. JAMA Neurol 76(12):1474–1483
18. Krajnc N et al (2022) Peripheral hemolysis in relation to iron rim presence and brain volume in multiple sclerosis. Front Neurol 13:928582
19. Berger JR (2017) Classifying PML risk with disease modifying therapies. Mult Scler Relat Disord 12:59–63
20. Jakimovski D et al (2020) Long-term drug treatment in multiple sclerosis: safety success and concerns. Expert Opin Drug Saf 19(9):1121–1142
21. Filippi M et al (2022) Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. J Neurol 269(10):5382–5394
22. Roberts JI et al (2025) Approach to Managing the Initial Presentation of Multiple Sclerosis: A Worldwide Practice Survey. Neurol Clin Pract 15(1):e200376
23. La Rosa F et al (2022) Cortical lesions, central vein sign, and paramagnetic rim lesions in multiple sclerosis: Emerging machine learning techniques and future avenues. Neuroimage Clin 36:103205
24. Page MJ et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
25. Thompson AJ et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17(2):162–173
26. Dal-Bianco A et al (2021) Iron rims in patients with multiple sclerosis as neurodegenerative marker? A 7-tesla magnetic resonance study. Front Neurol 12:632749
27. Wittayer M et al (2023) Cerebrospinal fluid-related tissue damage in multiple sclerosis patients with iron rim lesions. Mult Scler 29(4–5):549–558
28. Wittayer M et al (2023) Exploring (peri-) lesional and structural connectivity tissue damage through T1/T2-weighted ratio in iron rim multiple sclerosis lesions. Magn Reson Imaging 95:12–18
29. Wittayer M et al (2022) Spatial distribution of multiple sclerosis iron rim lesions and their impact on disability. Mult Scler Relat Disord 64:103967
30. Weber CE et al (2022) Long-term dynamics of multiple sclerosis iron rim lesions. Mult Scler Relat Disord 57:103340
31. Altokhis AI et al (2022) Longitudinal clinical study of patients with iron rim lesions in multiple sclerosis. Mult Scler J 28(14):2202–2211
32. Weber CE et al (2022) Association of iron rim lesions with brain and cervical cord volume in relapsing multiple sclerosis. Eur Radiol 32(3):2012–2022

33. Wenzel N et al (2023) Multiple sclerosis iron rim lesions are linked to impaired cervical spinal cord integrity using the T1/T2-weighted ratio. J Neuroimaging 33(2):240–246
34. Hu H et al (2022) The heterogeneity of tissue destruction between iron rim lesions and non-iron rim lesions in multiple sclerosis: A diffusion MRI study. Mult Scler Relat Disord 66:104070
35. Kim S et al (2023) Iron rim lesions as a specific and prognostic biomarker of multiple sclerosis: 3T-based susceptibility-weighted imaging. Diagnostics 13(11)
36. Wang X et al (2023) Enlarged choroid plexus related to iron rim lesions and deep gray matter atrophy in relapsing-remitting multiple sclerosis. Mult Scler Relat Disord 75:104740
37. Maggi P et al (2023) B cell depletion therapy does not resolve chronic active multiple sclerosis lesions. EBioMedicine 94:104701
38. Elliott C et al (2023) Lesion-level correspondence and longitudinal properties of paramagnetic rim and slowly expanding lesions in multiple sclerosis. Mult Scler J 29(6):680–690
39. Pontillo G et al (2023) Clinical correlates of R1 relaxometry and magnetic susceptibility changes in multiple sclerosis: a multiparameter quantitative MRI study of brain iron and myelin. Eur Radiol 33(3):2185–2194
40. Clark KA et al (2023) Early magnetic resonance imaging features of new paramagnetic rim lesions in multiple sclerosis. Ann Neurol 94(4):736–744
41. Sandi D et al (2021) Neurodegeneration in multiple sclerosis: symptoms of silent progression, biomarkers and neuroprotective therapy—kynurenines are important players. Molecules 26. https://doi.org/10.3390/molecules26113423.
42. Absinta M et al (2021) A lymphocyte–microglia–astrocyte axis in chronic active multiple sclerosis. Nature 597(7878):709–714
43. Reeves JA et al (2023) Paramagnetic rim lesions are associated with greater incidence of relapse and worse cognitive recovery following relapse. Mult Scler 29(8):1033–1038
44. Haider L et al (2014) Multiple sclerosis deep grey matter: the relation between demyelination, neurodegeneration, inflammation and iron. J Neurol Neurosurg Psychiatry 85(12):1386–1395
45. Xie Y et al (2024) The impact of paramagnetic rim lesions on cortical thickness and gray to white matter contrast in relapsing-remitting multiple sclerosis. Quant Imaging Med Surg 14(3):2614–2626
46. Rudko DA et al (2014) Multiple sclerosis: improved identification of disease-relevant changes in gray and white matter by using susceptibility-based MR imaging. Radiology 272(3):851–864
47. Pontillo G et al (2021) Unraveling Deep Gray Matter Atrophy and Iron and Myelin Changes in Multiple Sclerosis. AJNR Am J Neuroradiol 42(7):1223–1230
48. Lou C et al (2021) Fully automated detection of paramagnetic rims in multiple sclerosis lesions on 3T susceptibility-based MR imaging. Neuroimage Clin 32:102796
49. Comabella M et al (2021) CSF chitinase 3-like 1 is associated with iron rims in patients with a first demyelinating event. Mult Scler J 28(1):71–81

Authors and Affiliations

Nogol Motamedgorji[1] · Ashkan Bahrami[2] · Hayder jasim Taher[3] · Ahmed Mohamedbaqer Easa[4] · Sadaf Salehi[1] · Armin Tafazolimoghadam[5] · Mahan Farzan[6,7] · Zohreh Sadeghi[8] · Saharnaz Mofidinaeini[5] · Ramtin Hajibeygi[5,9] · Yaser Khakpour[10] · Mobina Fathi[11] · Anahita Zoghi[12] · Long H. Tu[9]

✉ Anahita Zoghi
anahita.zoghi@gmail.com

✉ Long H. Tu
long.tu@yale.edu

Nogol Motamedgorji
nogolgorji@gmail.com

Ashkan Bahrami
ashkanbahrami1998@gmail.com

Hayder jasim Taher
haiderdr75@gmail.com

Ahmed Mohamedbaqer Easa
ahmedeasa1985@gmail.com

Sadaf Salehi
salehisadafmd@gmail.com

Armin Tafazolimoghadam
armintafazolim@gmail.com

Mahan Farzan
mahanfarzan.iri@gmail.com

Zohreh Sadeghi
Zohre.sadeghi.a@gmail.com

Saharnaz Mofidinaeini
Saharnaz.mn@gmail.com

Ramtin Hajibeygi
ramtin.hajibeygi@yale.edu

Yaser Khakpour
y.khm888@gmail.com

Mobina Fathi
fathi.mobina78@gmail.com

[1] Student Research Committee, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran

[2] Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran

[3] Department of Radiological Technologies, College of Health and Medical Technologies, University of Hilla, Babylon, Iraq

[4] Department of Radiology Technology, Collage of Health and Medical Technology, Al-Ayen Iraqi University, Thi-Qar, 64001, Iraq

[5] School of Medicine, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran

[6] Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Islamic Republic of Iran

[7] Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Islamic Republic of Iran

[8] Department of Radiology, Imam Khomeini Hospital Complex, Tehran, Islamic Republic of Iran

[9] Department of Radiology and Biomedical Imaging, Yale School of Medicine, CT, United States

[10] Faculty of Medicine, Guilan University of Medical Science, Rasht, Guilan, Islamic Republic of Iran

[11] Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

[12] Neurology Department, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran