Immunometabolic Crosstalk at the Blood-Brain Barrier in Multiple Sclerosis: Monocytes, HDL Dysfunction, and Accessible Biomarkers of Neuroinflammatory Burden

Alaa Abdullah Abd Elmotaleb Mohammed, Mahmoud Elsayed Alebiary, Wael Mahmoud Elsayed, Sabah Elsayed Fathy

Neurology Department, Faculty of Medicine, Zagazig University, Egypt
Corresponding Author: Alaa Abdullah Abd Elmotaleb Mohammed

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Multiple sclerosis arises from an evolving interaction between peripheral immunity and compartmentalized central nervous system injury. Monocytes and monocyte-derived macrophages participate in leukocyte recruitment, blood-brain barrier disruption, myelin phagocytosis, cytokine production, oxidative injury, and tissue remodeling. High-density lipoprotein is equally relevant but biologically more complex than its routine cholesterol concentration suggests. Through apolipoprotein A-I, cholesterol-efflux pathways, paraoxonase activity, and endothelial signaling, functional HDL can restrain oxidation and inflammation; during sustained inflammatory stress, however, HDL may become dysfunctional. This immunometabolic opposition provides the rationale for combining the circulating monocyte count with HDL cholesterol as the monocyte-to-HDL ratio. Early studies associate a higher ratio with greater multiple-sclerosis disability, but the ratio cannot identify the cellular source of central nervous system injury or distinguish acute inflammatory activity from accumulated damage and progression. The same value may result from monocytosis, reduced HDL cholesterol, or both, and is readily modified by infection, obesity, smoking, corticosteroids, statins, and disease-modifying therapy. A clinically coherent biomarker strategy should therefore organize markers by biological layer: systemic inflammatory context, barrier and lesion activity, neuroaxonal injury, astroglial response, and functional outcome. Within that architecture, the monocyte-to-HDL ratio is best positioned as a low-cost contextual signal that may complement, but cannot replace, magnetic resonance imaging, serum neurofilament light chain, glial fibrillary acidic protein, and longitudinal neurological assessment.

Keywords: Multiple sclerosis; monocytes; high-density lipoprotein; blood-brain barrier; oxidative stress; immunometabolism

Introduction

Multiple sclerosis (MS) is not adequately described as a purely peripheral autoimmune attack or a purely degenerative brain disorder. Focal lymphocytic inflammation, monocyte and macrophage activity, microglial responses, astrocytosis, demyelination, and axonal injury coexist in changing proportions. Early relapsing disease commonly displays blood-brain barrier (BBB) permeability and new focal lesions, whereas progressive disease is increasingly dominated by chronic active lesions, diffuse tissue damage, cortical pathology, and inflammation retained within the central nervous system (CNS). The biology is continuous even when clinical phenotypes appear discrete. [1,2]

This evolving pathophysiology creates a biomarker problem. A marker that tracks peripheral leukocyte activation may be most informative during inflammatory activity but less sensitive to smoldering compartmentalized injury. Conversely, a protein released by damaged axons may show that injury has occurred without identifying its mechanism. The BBB sits between these domains and should be understood as an active neurovascular interface rather than a passive wall. Endothelial cells, pericytes, astrocytic endfeet, basement membrane, and immune cells together regulate trafficking and tissue homeostasis. [3,4]

Current diagnosis still depends on a compatible clinical context and demonstration of lesion dissemination, increasingly supported by specific MRI and cerebrospinal-fluid features. The 2024 McDonald criteria improve the use of optic-nerve evidence, the central vein sign, paramagnetic rim lesions, and kappa free light chains in appropriate circumstances. These diagnostic advances do not eliminate the need for monitoring tools that separate acute activity, tissue injury, and progression. Routine blood indices are appealing precisely because they are available repeatedly, but accessibility must not be confused with biological specificity. [5,6]

Aim

To synthesize how monocyte biology, HDL function, oxidative stress, and blood-brain barrier dysfunction intersect in multiple sclerosis, and to position MHR within a layered framework of clinically meaningful biomarkers.

The Peripheral-Central Immune Continuum

Experimental studies established that inflammatory monocytes expand in blood before clinical autoimmune demyelination, migrate into the CNS, and acquire pathogenic effector functions. King et al. demonstrated that circulating Ly-6C-high myeloid precursors entered the CNS and promoted autoimmune demyelinating disease. Yamasaki et al. later separated infiltrating monocyte-derived macrophages from resident microglia and showed distinct functional programs: monocyte-derived cells were strongly associated with inflammatory demyelination, whereas microglial responses were more closely linked to debris processing and local tissue adaptation. Translation to human MS requires caution, but the work explains why a peripheral monocyte signal may have mechanistic relevance. [7,8]

Entry into the CNS depends on coordinated endothelial activation, chemokine gradients, adhesion, and transendothelial migration. Barrier-tightening experiments provide proof of principle that modifying the neurovascular interface can reduce leukocyte passage and parenchymal damage. Laquinimod, for example, enhanced experimental CNS barrier properties and reduced migration of inflammatory lymphocyte populations. Such studies do not validate monocyte count as a direct BBB marker, but they place circulating immune cells within a regulated trafficking pathway rather than treating their concentration as an isolated laboratory observation. [9]

Endothelial Activation and the Neurovascular Unit

The neurovascular unit integrates endothelial cells, pericytes, astrocytes, neurons, extracellular matrix, and circulating blood elements. Inflammatory cytokines increase endothelial adhesion molecules and chemokines, while oxidative injury and protease activity weaken junctional integrity. Activated monocytes can adhere, crawl, and traverse this interface, but the process is selective and locally regulated. Peripheral monocytosis alone is therefore insufficient to infer BBB passage; trafficking also depends on cellular phenotype, receptor expression, endothelial state, and regional chemokine signals. [4,7,9]

Gadolinium enhancement represents one consequence of barrier permeability, not the entire neurovascular response. Subtle endothelial dysfunction may occur without visible enhancement, while chronic progressive injury may continue after overt permeability declines. This helps explain why systemic inflammatory indices can correlate with disease in one cohort and fail in another. The sampled population may differ in the proportion of acute lesions, treated relapsing disease, chronic active lesions, and progression independent of relapse activity. A biomarker study that does not characterize MRI timing and phenotype cannot resolve these sources of heterogeneity. [2,3]

Vascular comorbidity can further disturb the neurovascular unit. Smoking, hypertension, diabetes, obesity, and dyslipidemia influence endothelial function and innate immunity, and they may reduce neurological reserve. These factors can raise MHR even if focal MS inflammation is unchanged. Their presence does not make the ratio clinically irrelevant; it changes its interpretation from a putative disease-specific marker to a broader measure of adverse immunometabolic context. [5]

Monocyte Heterogeneity and Lesion Biology

Human monocytes are commonly divided into classical, intermediate, and nonclassical subsets according to CD14 and CD16 expression. These subsets differ in chemokine receptors, endothelial interaction, cytokine production, antigen presentation, and vascular surveillance. Routine complete blood counts collapse them into one absolute number. Two patients with identical monocyte counts may therefore have different inflammatory phenotypes, and the relationship between blood subsets and tissue macrophages changes with relapse, treatment, age, and comorbidity. MHR cannot resolve this heterogeneity. [1,8]

Within active MS plaques, myelin-laden macrophages are prominent and correlate with areas of tissue damage. Their actions are not uniformly harmful. Phagocytosis removes inhibitory myelin debris, and macrophage polarization can support repair under appropriate conditions. In chronic active lesions, however, activated microglia and macrophages at expanding rims are associated with continuing axonal injury. A higher circulating monocyte-derived index may thus reflect one component of an inflammatory environment, but it cannot determine whether CNS myeloid cells are destructive, reparative, or compartmentalized behind a largely restored BBB. [1,2]

Myelin Debris, Repair, and the Limits of a Pro-Inflammatory Label

Efficient remyelination requires clearance of damaged myelin, recruitment and differentiation of oligodendrocyte precursor cells, axonal viability, and a permissive metabolic environment. Myeloid cells participate in each step. Early pro-inflammatory activity may contribute to tissue injury, whereas later phagocytic and trophic programs can support

repair. A single peripheral monocyte count cannot distinguish these temporally ordered functions. Describing every monocyte increase as harmful oversimplifies lesion biology and can lead to inappropriate causal claims for MHR. [1,8,10]

Lipid handling links debris clearance to immune phenotype. Macrophages that ingest myelin acquire a large cholesterol burden and depend on efflux pathways to restore cellular homeostasis. Functional HDL can accept cholesterol through apolipoprotein A-I-dependent mechanisms in peripheral tissues, while dysfunctional HDL may impair this regulatory route. The exact relevance of peripheral HDL to CNS macrophages remains uncertain because brain lipid metabolism is compartmentalized. MHR is therefore best understood as a systemic analogue of an immunometabolic balance, not a direct measurement of cholesterol removal from MS lesions. [10,11]

Repair capacity also varies with age, lesion location, disease duration, and therapy. An elevated ratio in a patient with longstanding progressive disease may reflect comorbidity more than ongoing lesion expansion, whereas the same value during an untreated inflammatory relapse may accompany active leukocyte trafficking. Biomarker interpretation should consequently incorporate the phase of disease rather than assuming one mechanism across the MS spectrum. [2,3]

Cholesterol Homeostasis, Myelin, and HDL

Cholesterol is a major structural constituent of myelin, and oligodendrocytes require tightly regulated lipid synthesis and trafficking for membrane expansion. Experimental limitation of cholesterol synthesis impairs myelin growth, demonstrating that cholesterol is not merely a cardiovascular risk variable in neurology. Nevertheless, peripheral lipoprotein concentrations do not directly represent CNS cholesterol availability because brain cholesterol is largely synthesized locally and exchange across the intact BBB is restricted. The relevance of circulating HDL in MS therefore lies mainly in its vascular, antioxidant, and immunoregulatory actions rather than direct delivery of cholesterol to myelin. [10]

Functional HDL supports cholesterol efflux from macrophages through apolipoprotein A-I and ATP-binding cassette transporters, limits oxidation of lipids, carries paraoxonase-1, and reduces endothelial activation. These actions can alter membrane lipid rafts, innate immune signaling, nitric oxide bioavailability, and leukocyte adhesion. In relapsing-remitting MS, altered HDL composition and impaired function have been demonstrated even when conventional lipid measurements do not fully explain the abnormality. This is a critical limitation of any ratio that uses HDL-C as its denominator. [11]

Dysfunctional HDL and Oxidative Stress

Inflammation changes HDL cargo and enzymatic performance. Oxidation of apolipoprotein A-I can impair cholesterol efflux, while reduced paraoxonase activity weakens protection against lipid peroxidation. Patients with MS have shown increased lipid hydroperoxides and altered paraoxonase-related measures, supporting systemic oxidative stress. These observations make low HDL-C only one possible abnormality; a normal or high HDL-C concentration may coexist with particles that function poorly. [12,13,14]

The clinical importance of HDL quality was illustrated in optic neuritis. Vural et al. found no significant difference in HDL-C concentration between affected patients and controls, yet paraoxonase activity was lower and the myeloperoxidase-to-paraoxonase ratio was higher in the MS group. The dysfunctional-HDL index correlated strongly with delayed P100 latency. The study was small and cross-sectional, but it demonstrates why concentration-based indices should not be interpreted as complete measures of HDL biology. [12]

Oxidative Stress as a Shared Mechanistic Bridge

Oxidative stress can connect monocyte activation, endothelial dysfunction, HDL remodeling, mitochondrial injury, and axonal vulnerability. Activated myeloid cells generate reactive species, while oxidized lipids and damaged proteins amplify innate immune signaling. HDL-associated antioxidant systems can buffer part of this burden, but inflammatory remodeling reduces their effectiveness. The opposing numerator and denominator of MHR therefore fit a coherent mechanistic narrative, although the ratio itself does not measure reactive oxygen species, lipid peroxidation, or antioxidant capacity. [11,13,14]

This distinction matters when interpreting therapeutic response. A treatment may lower relapse activity by restricting lymphocyte trafficking or depleting B cells without producing a parallel change in monocyte count or HDL-C. Conversely, weight loss, smoking cessation, exercise, or statin treatment may improve the ratio without altering CNS inflammatory lesions. MHR may respond to clinically beneficial systemic change, but change in the biomarker cannot be assumed to mediate change in MS. [5,15,16]

The Blood-Brain Barrier as an Immunometabolic Interface

BBB disruption permits plasma proteins and activated leukocytes to access the CNS, while inflammatory mediators from the CNS can influence the systemic compartment. Monocyte-endothelial interactions, oxidative stress, matrix

metalloproteinases, and cytokines can weaken tight junctions and promote trafficking. HDL-associated endothelial support could theoretically counter part of this process through nitric oxide signaling and reduced adhesion, but direct evidence linking routine HDL-C or MHR to human BBB permeability in MS remains limited. Mechanistic plausibility should not be presented as clinical validation. [4,9]

Barrier behavior also changes with disease stage. Gadolinium enhancement is an informative marker of focal BBB permeability, but progressive MS may continue to worsen when enhancement is sparse. Chronic active lesions, meningeal inflammation, and diffuse microglial activation can persist within the CNS compartment. A peripheral ratio may therefore be more responsive to systemic inflammatory activity than to progression independent of relapse activity. This stage dependence must be built into study design and interpretation. [2,3]

From Two Components to a Composite Ratio

MHR combines an absolute monocyte count with HDL-C. The numerator represents the available circulating monocyte pool, whereas the denominator is treated as a proxy for anti-inflammatory and antioxidant capacity. A rising ratio can result from increased monocytes, reduced HDL-C, or simultaneous movement in both directions. The composite may strengthen a signal when both components reflect the same inflammatory state, but it can also obscure distinct mechanisms. Reporting only the ratio without its two components prevents meaningful interpretation. [15,16]

The principal MS-specific study by Ulusoy et al. associated higher MHR with disease severity and disability. The supplied Zagazig University thesis reported a compatible pattern, including higher MHR in patients than controls and a stepwise rise across disability categories. These convergent findings support further research, but the samples were small and cross-sectional. Neither study demonstrates that baseline MHR predicts a future relapse, MRI lesion, confirmed disability worsening, or treatment failure. [17,18]

Table 1. Interpreting the biological patterns that can produce an elevated MHR

Monocytes	HDL-C	Possible interpretation	Important alternatives
High	Normal	Predominantly cellular inflammatory signal	Infection, smoking, steroid timing, myeloid redistribution
Normal	Low	Predominantly metabolic or lipoprotein signal	Obesity, diabetes, diet, genetic HDL phenotype, statin exposure
High	Low	Concordant inflammatory-metabolic imbalance	Systemic illness or combined comorbidity may dominate
Normal	Normal	Low ratio does not exclude CNS activity	Compartmentalized inflammation or silent progression

Activity, Damage, and Progression Are Different Targets

Clinical disability is most often summarized by EDSS, which provides a common neurological language but becomes strongly dependent on ambulation at higher scores. MSSS relates EDSS to disease duration and helps describe relative severity, yet it remains influenced by cohort structure and timing. Biomarker correlations with EDSS may therefore reflect accumulated disease burden, age, duration, or phenotype rather than current inflammatory activity. Studies of MHR should not label a cross-sectional EDSS association as prediction of progression. [19,20]

Modern disease descriptors emphasize activity and progression as modifiers across phenotypes. Relapse and new MRI lesions indicate inflammatory activity, while confirmed disability worsening may occur with or without relapse. A useful study should predefine the target: relapse within a time window, new or enlarging T2 lesions, gadolinium enhancement, confirmed disability worsening, or progression independent of relapse activity. Combining these outcomes into a single category weakens biological interpretation and encourages nonportable cutoffs. [21]

Disease-Modifying Therapy as a Biological Perturbation

Disease-modifying therapies alter the cellular compartments that MHR attempts to summarize. Corticosteroids acutely redistribute leukocytes; sphingosine-1-phosphate receptor modulators sequester lymphocytes; anti-CD20 therapies deplete B cells; natalizumab inhibits leukocyte trafficking; and immune-reconstitution strategies reshape circulating populations over time. Although monocytes are not the principal target of every therapy, treatment changes the inflammatory network and can modify the relationship between peripheral counts and CNS activity. Analyses that pool therapies without timing information risk confounding by indication and mechanism. [5,21]

Treatment selection is itself associated with disease severity. Patients with aggressive or active disease are more likely to receive high-efficacy therapy, while older patients with progressive disease may have different treatment exposure and comorbidity. A cross-sectional association between MHR and disability can therefore be distorted in either direction. Stratification by therapy class, adjustment for treatment duration, and sensitivity analysis around recent steroids are minimum requirements for credible clinical studies. [17,18]

Longitudinal sampling around treatment initiation could be especially informative. If MHR falls after suppression of inflammatory activity and that change precedes reduced MRI activity, the ratio may have monitoring value. If it remains unchanged while established measures improve, the marker may primarily reflect background metabolic inflammation. Both outcomes are scientifically useful because they define the biological layer represented by MHR. [17]

A Layered Biomarker Architecture

MRI provides spatial evidence of lesion distribution, inflammatory activity, tissue loss, and chronic lesion characteristics. Conventional T2 and gadolinium-enhanced imaging remains central, while susceptibility-sensitive sequences add information through the central vein sign and paramagnetic rim lesions. MRI is nevertheless intermittent, costly, and imperfectly related to clinical status. Peripheral biomarkers should be designed to complement this spatial information, not compete with it as if both measured the same process. [22,23]

Serum neurofilament light chain (sNfL) reflects neuroaxonal injury and is sensitive to recent inflammatory activity. In large cohorts, age- and body-mass-index-adjusted sNfL Z scores predicted future clinical or MRI activity better than raw concentrations. Serum glial fibrillary acidic protein (sGFAP) appears more closely related to astroglial activation and future progression independent of relapse activity. These markers occupy different biological layers from MHR, which is more plausibly a measure of systemic context. [24,25,26]

Routine markers remain useful because they are inexpensive and frequently repeated. NLR has been associated with MS and disease activity in several cohorts, but findings are not uniform. Serial CRP and other inflammatory markers have often shown weak relationships with short-term progression. Their main value may lie in identifying systemic inflammatory states, comorbidity, or discordance that prompts further evaluation. MHR should be held to the same standard and should not be promoted simply because it is readily calculated. [27,28]

Table 2. Positioning MHR within a layered MS biomarker framework

Biological layer	Representative measure	Principal information	Main limitation
Systemic context	MHR, NLR, CRP	Peripheral inflammatory or metabolic milieu	Low CNS specificity
Barrier/lesion activity	Gadolinium enhancement, new T2 lesions	Focal inflammatory activity and BBB permeability	Intermittent assessment
Neuroaxonal injury	Serum NfL	Recent or ongoing axonal damage	Age, BMI, renal function and comorbidity affect levels
Astroglial response	Serum GFAP	Astrogliosis and progression-related biology	Assay and threshold standardization still evolving
Functional outcome	EDSS, performance tests, cognition	Patient-level neurological effect	Domain weighting and delayed change

Clinical Interpretation in Resource-Variable Settings

In settings where advanced biomarker assays are not routinely available, MHR may be useful as part of a low-cost longitudinal profile that also includes symptoms, examination, EDSS, relapse history, treatment exposure, CBC, CRP, and lipid profile. The safest use is contextual: an unexpected increase should trigger assessment for infection, corticosteroid exposure, smoking, metabolic disease, medication change, and possible MS activity. It should not independently trigger diagnosis or escalation of disease-modifying therapy. [5,17]

A single universal cutoff is unlikely to transfer across laboratories and populations. Monocyte units, HDL assay methods, fasting policy, sex distribution, obesity prevalence, smoking, statin use, and therapy mix all change the ratio. Cardiovascular MHR literature demonstrates broad prognostic associations but cannot supply an MS-specific

threshold. Local reference distributions may help quality control, yet clinically meaningful thresholds require prospective derivation and external validation against neurological outcomes. [29]

Longitudinal Interpretation and Within-Person Baselines

Population reference ranges are useful for describing distributions, but within-person change may be more relevant for a variable influenced by metabolic phenotype. Serial MHR should be collected under comparable conditions and interpreted with the two component values. A rise caused by increasing monocytes during infection differs from a rise caused by falling HDL-C during weight gain or endocrine disease. Component-level review prevents the ratio from concealing the clinical explanation. [17,18]

The interval between measurements should reflect the intended use. Short intervals may capture relapse-associated or treatment-related changes but are vulnerable to transient biological variation; long intervals may be more suitable for cardiometabolic context but can miss acute inflammatory activity. Studies should quantify within-person variability, define a meaningful change threshold, and relate the timing of blood sampling to MRI and confirmed clinical events. Repeating an unstandardized ratio more frequently does not automatically improve monitoring. [24,26]

A low-cost biomarker can improve equity only if it is interpreted safely. In regions with limited MRI access, an abnormal MHR might help prioritize evaluation, but a normal ratio must not delay imaging or specialist review when symptoms suggest relapse. Algorithms should include infection screening, metabolic assessment, and clear escalation criteria. The purpose is to organize uncertainty, not to replace neurological judgment with a laboratory cutoff. [5,6]

Research Priorities

Future studies should enroll sufficiently large, phenotype-diverse cohorts and collect MHR at standardized intervals outside acute infection and recent corticosteroid use. Both monocyte count and HDL-C must be reported alongside the ratio. Prespecified analyses should adjust for age, sex, body mass index, smoking, diabetes, lipid-lowering therapy, disease duration, relapse status, MRI activity, and disease-modifying therapy. Repeated-measures models are preferable to isolated cross-sectional comparisons because they can distinguish within-person change from between-person metabolic differences. [17,18]

The decisive test is incremental value. MHR should improve prediction beyond clinical variables, MRI, and established biomarkers, with calibration and decision-curve analyses reported in an external cohort. Mechanistic substudies could add monocyte phenotyping, HDL particle number, cholesterol-efflux capacity, paraoxonase activity, and BBB-related imaging. Such work would determine whether MHR is merely a convenient arithmetic association or a stable window into clinically relevant immunometabolic activity. [11,24,25]

References

1. Attfield KE, Jensen LT, Kaufmann M, Friese MA, Fugger L. The immunology of multiple sclerosis. Nat Rev Immunol. 2022;22(12):734-750.
2. Lassmann H. Multiple sclerosis pathology. Cold Spring Harb Perspect Med. 2018;8(3):a028936.
3. Correale J, Gaitan MI, Ysrraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain. 2017;140(3):527-546.
4. Silva RV, Morr AS, Mueller S, et al. Contribution of tissue inflammation and blood-brain barrier disruption to brain softening in a mouse model of multiple sclerosis. Front Neurosci. 2021;15:701308.
5. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. JAMA. 2021;325(8):765-779.
6. Montalban X, Lebrun-Frenay C, Oh J, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. Lancet Neurol. 2025;24(10):850-865.
7. King IL, Dickendesher TL, Segal BM. Circulating Ly-6C-positive myeloid precursors migrate to the CNS and play a pathogenic role during autoimmune demyelinating disease. Blood. 2009;113(14):3190-3197.
8. Yamasaki R, Lu H, Butovsky O, et al. Differential roles of microglia and monocytes in the inflamed central nervous system. J Exp Med. 2014;211(8):1533-1549.
9. Luhder F, Kebir H, Odoardi F, et al. Laquinimod enhances central nervous system barrier functions. Neurobiol Dis. 2017;102:60-69.
10. Saher G, Brugger B, Lappe-Siefke C, et al. High cholesterol level is essential for myelin membrane growth. Nat Neurosci. 2005;8(4):468-475.
11. Jorissen W, Wouters E, Bogie JF, et al. Relapsing-remitting multiple sclerosis patients display an altered lipoprotein profile with dysfunctional HDL. Sci Rep. 2017;7:43410.

12. Vural G, Gumusyayla S, Karakoyunlu Eren F, et al. Relationship between pattern reversal visual evoked potential P100 wave latency and dysfunctional HDL in patients with multiple sclerosis subjected to an optic neuritis attack: a case-control study. Medicine (Baltimore). 2024;103(6):e37115.
13. Ferretti G, Bacchetti T, Principi F, et al. Increased levels of lipid hydroperoxides in plasma of patients with multiple sclerosis: a relationship with paraoxonase activity. Mult Scler. 2005;11(6):677-682.
14. Castellazzi M, Trentini A, Romani A, et al. Decreased arylesterase activity of paraoxonase-1 (PON-1) might be a common denominator of neuroinflammatory and neurodegenerative diseases. Int J Biochem Cell Biol. 2016;81(Pt B):356-363.
15. Weinstock-Guttman B, Zivadinov R, Mahfooz N, et al. Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. J Neuroinflammation. 2011;8:127.
16. Lorincz B, Vrablik M, Murali R, et al. Lipid and brain volumetric measures in multiple sclerosis patients: findings from a large observational study. Acta Neurol Belg. 2024;124(6):1981-1988.
17. Ulusoy EK, Bolatturk OF, Gol MF. Relation between the novel marker monocyte to high-density lipoprotein cholesterol ratio and severity in multiple sclerosis. Ann Indian Acad Neurol. 2020;23(3):275-279.
18. Mohammed AAAE. Monocytes to High Density Lipoprotein Ratio as a Novel Marker for Disease Severity in Multiple Sclerosis Patients [master's thesis]. Zagazig, Egypt: Zagazig University; 2026.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-1452.
20. Roxburgh RHSR, Seaman SR, Masterman T, et al. Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. Neurology. 2005;64(7):1144-1151.
21. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278-286.
22. Filippi M, Bruck W, Chard D, et al. Association between pathological and MRI findings in multiple sclerosis. Lancet Neurol. 2019;18(2):198-210.
23. Barkhof F, Calabresi PA, Miller DH, et al. 2024 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in the diagnosis of multiple sclerosis. Lancet Neurol. 2025;24(10):866-879.
24. Benkert P, Meier S, Schaedelin S, et al. Serum neurofilament light chain for individual prognostication of disease activity in people with multiple sclerosis: a retrospective modelling and validation study. Lancet Neurol. 2022;21(3):246-257.
25. Meier S, Willemse EAJ, Schaedelin S, et al. Serum glial fibrillary acidic protein compared with neurofilament light chain as a biomarker for disease progression in multiple sclerosis. JAMA Neurol. 2023;80(3):287-297.
26. Disanto G, Barro C, Benkert P, et al. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann Neurol. 2017;81(6):857-870.
27. Demirci S, Demirci S, Kutluhan S, Koyuncuoglu HR, Yurekli VA. The clinical significance of the neutrophil-to-lymphocyte ratio in multiple sclerosis. Int J Neurosci. 2016;126(8):700-706.
28. Giovannoni G, Miller DH, Losseff NA, et al. Serum inflammatory markers and clinical/MRI markers of disease progression in multiple sclerosis. J Neurol. 2001;248(6):487-495.
29. Ganjali S, Gotto AM Jr, Ruscica M, et al. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. J Cell Physiol. 2018;233(12):9237-9246.