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REVIEW

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miR-146a and miR-155 as promising biomarkers for prognosis and diagnosis of multiple sclerosis: systematic review

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Abstract

Background Small RNA molecules known as microRNAs (miRNAs) regulate gene expression during the post-translational steps. miRNAs are essential for many physiological processes, such as cell division, growth, and proliferation, as well as development and metabolism.

Aims To review the developments in investigations on miR-155 and miR-146a as possible biomarkers for multiple sclerosis (MS) disease diagnosis and prognosis.

Methods A comprehensive analysis of the available literature was carried out by searching databases including PubMed, Scopus, and Web of Science for papers published between 2011 and 2023 years. Only original articles written in the English language were considered for inclusion in this review.

Results A total of 29 studies were initially identified, with 14 meeting the inclusion criteria.

Conclusion The present study underscores the crucial role of microRNAs, particularly miR-155 and miR-146a, in the etiology and progression of multiple sclerosis (MS). Through an extensive analysis of the literature, we have found compelling evidence linking aberrations in the expression and function of these microRNAs to MS pathogenesis. Specifically, our synthesis suggests that miR-155 and miR-146a hold promise as valuable biomarkers for both the diagnosis and prognosis of MS. Despite the challenges posed by the heterogeneity of MS subtypes, the non-invasive accessibility of miRNAs in various bodily fluids, including serum, peripheral blood, cerebrospinal fluid, and extracellular vesicles, presents a promising avenue for the development of robust diagnostic and prognostic tools. By elucidating the intricate roles of miR-155 and miR-146a in MS, our findings contribute to advancing our understanding of the disease mechanisms and pave the way for the development of more effective diagnostic and therapeutic strategies.

Keywords Multiple sclerosis (MS), MicroRNAs, Biomarkers, Prognosis

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Introduction

Multiple sclerosis (MS) is categorized as an autoimmune disease, and its symptoms include degeneration, inflammation, and demyelination of the central nervous system (CNS) [1]. This disease mainly affects people in the early stages of adulthood, affecting their functioning, finances, and overall quality of life. Many studies on the pathophysiology of MS have determined that environmental factors, genetic factors, and lifestyle factors such as smoking play a role in the pathogenesis of this disease [2]. Based on previous research, it is estimated that the prevalence of MS in the world in 2020 will be equal to 2.8 million people [1, 3]. The prevalence of immunodeficiency diseases is higher in women relative to men, and MS is no exception, with a female-to-male ratio of 3:1 [4, 5]. The clinical diagnosis of MS is made using a combination of laboratory, clinical, and imaging techniques. Clinical specialties can exclude other neurological diseases with similar phenotypes using magnetic resonance imaging (MRI) technology based on McDonald's diagnostic procedure and help in the diagnosis of the disease [6–8]. However, MRI imaging technology is not able to fully reflect disease mechanisms such as activation of microglia and destruction of the CNS. Due to the increasing prevalence of MS worldwide because of lifestyle, environmental, and genetic factors, early diagnosis of this disease can be effective in reducing treatment costs and enhancing the well-being of individuals impacted by it [3, 6]. According to studies conducted at the global level, the most important factors that delay the diagnosis of MS in many countries include the lack of accurate diagnostic tests and sufficient laboratory facilities [7]. Therefore, it is imperative to investigate alternative diagnostic and prognostic approaches utilizing biomarkers that are capable of accurately and sensitively identifying the clinical features of multiple sclerosis, thereby aiding in the prognosis of this debilitating condition [8]. Aberrations in the production of particular microRNAs can be potential biomarkers for the prognosis and diagnosis of MS, as recent progress in the assessment of the functions of microRNAs in the pathophysiology of MS disease has shown [9]. One of the most popular research areas in recent years for the utilization of microRNAs as biomarkers for prediction, diagnosis, and even treatment of this disease is changes in the patterns of expression and operational roles of microRNAs in biological samples of MS patients [10]. miRNAs regulate the post-translational patterns of gene expression and are crucial for a wide range of biological functions, such as cell formation, growth, proliferation, differentiation, and metabolism [11]. These small, noncoding RNA molecules, which are usually 20 to 22 nucleotides long, operate to regulate the stability of mRNA and govern the expression of genes. So far, based on various studies, a large number of different miRNAs have been discovered, whose number reaches more than 2500 miRNAs just in humans [12]. MicroRNAs have been linked to the pathogenesis of numerous diseases, including cancer, autoimmune diseases, infectious diseases, and neurological diseases, according to investigations [13–15]. It is known that miR-146a is an important molecule that regulates immune system inflammatory responses and suppresses inflammation. The adaptive and innate immune systems both heavily rely on miR-155, and a number of inflammatory disorders have been linked to abnormal regulation of this miRNA [16]. Assessing the progress in research regarding the possibility of miR-146a and miR-155 as prognostic and diagnostic biomarkers for MS was the primary aim of this review.

Search strategy

The search method used to find papers relevant to this study is as follows:

The PubMed, Scopus, and Web of Science databases were queried using relevant search terms and syntax proper for each database:

(("MicroRNAs"[Mesh]) AND (“Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis, Relapsing–Remitting"[Mesh] OR "Multiple Sclerosis, Chronic Progressive"[Mesh])) AND "MIRN155 microRNA, human" [Supplementary Concept] and (("MicroRNAs"[Mesh]) AND (“Multiple Sclerosis"[Mesh] OR "Multiple Sclerosis, Relapsing–Remitting"[Mesh] OR "Multiple Sclerosis, Chronic Progressive"[Mesh])) AND "MIRN146 microRNA, human" [Supplementary Concept].

A literature review diagram Based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) template was created (Fig. 1).

The reviewed publications for this study fall within the time frame of 2011 to 2023. Of the 29 articles in the review, 25 were original articles. However, three of these articles were not fully accessible, and only their abstracts were available, leading to their exclusion from this study. Additionally, eight papers were deemed unrelated to the study's aim and were therefore eliminated from this review. This left a total of 14 articles for examination in this review.

Results

mRNA expression of miR-146a and miR-155 in multiple sclerosis (MS) patients

In research published in 2022, Ashrafi et al. evaluated the expression patterns of miR-155 and miR-146a in peripheral blood monocellular cells (PBMCs) that were extracted from 75 RRMS patients and 75 healthy control subjects. Their primary objective was to examine

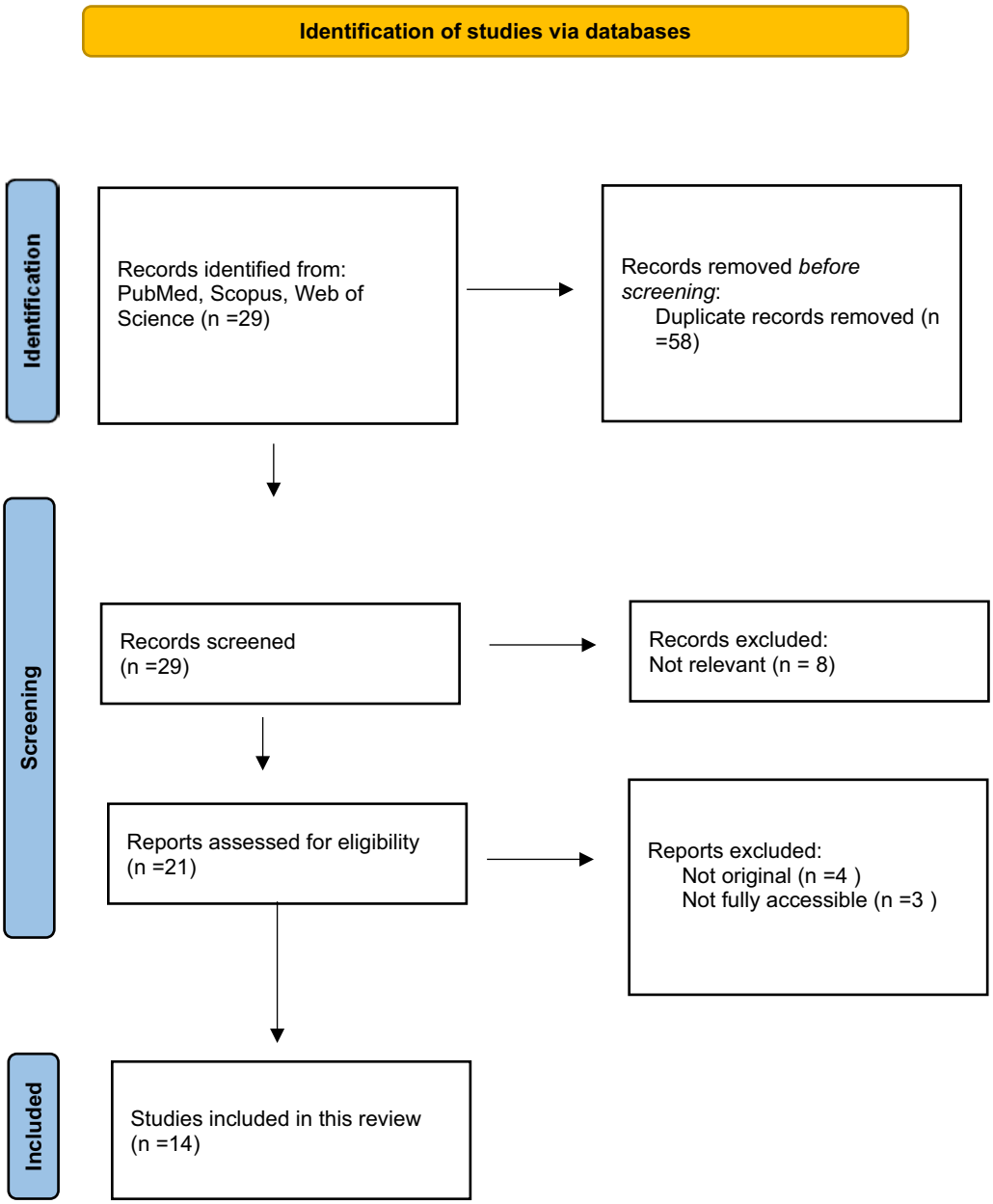

Fig. 1 Literature search strategy

the potential of these microRNAs as diagnostic markers for RRMS and to compare their levels between RRMS patients and healthy controls. They utilized the real-time polymerase chain reaction (RT-PCR) technique for their analysis. According to their results, relapsing–remitting multiple sclerosis (RRMS) patients had statistically significant lower levels of miRNA-155 than those in a control group. ($p = 0.005$) [17].

In a 2020 research investigation, Shademan et al. assessed the pattern of expression of miR-155 and miR-146a in both individuals diagnosed with MS and a control group of healthy participants. Their investigation's main objective was to realize whether these two microRNAs' expression levels and the onset of MS disease are correlated. The real-time polymerase chain reaction method was employed to analyze the levels of microRNAs extracted from the blood samples of 30 healthy participants and 30 patients diagnosed with multiple sclerosis. When comparing individuals with primary progressive multiple sclerosis (PPMS) to healthy control

subjects, it was revealed that PPMS patients expressed a higher level of miRNA-146a. Additionally, it was shown that, in comparison with healthy subjects, patients with secondary progressive multiple sclerosis (SPMS) had elevated levels of miRNA-146a expression. When RRMS patients were compared to the healthy control participants, it was revealed that their expression levels of miR-146a were higher ($p < 0.001$). The expression level of microRNA-155 was indicated to be increased in patients with PPMS in comparison with the healthy control group. ($p > 0.01$). In addition, microRNA-155 expression was elevated in SPMS patients compared to the control group ($p < 0.001$). In RRMS patients, microRNA-155 was upregulated compared to the control group ($p < 0.001$). The main constraint of their investigation was the limited size of their studied sample. Therefore, they recommended examining the expression level of these two microRNAs in larger statistical populations from other geographic locations and other races [18].

In 2016, Mameli et al. conducted an investigation to assess the expression profiles of various potential microRNAs, such as miR-155, miR-132, miR-146a, and miR-26a, isolated from peripheral blood mononuclear cells (PBMCs) of individuals with multiple sclerosis (MS) in comparison with those of healthy control subjects. Their investigation involved 26 patients with MS and 26 healthy participants. Through the use of the RT-PCR technique, their study indicated that the expression levels of miR-155 and miR-132 were increased in ten out of twenty-four MS patients [19].

mRNA expression of miR-146a in multiple sclerosis (MS) patients

Muñoz-San Martín et al. carried out another study in 2019 to assess the relationship between microRNAs in cell-free cerebrospinal fluid and gadolinium-enhancing (Gd+) lesions in 46 MS patients. The goal of their investigation was to evaluate the potential of these microRNAs as biomarkers in the pathophysiology of multiple sclerosis. They examined 28 candidate microRNAs using qPCR, and their results revealed that at least 75% of CSF samples included at least seven of the 28 candidate miRNAs—including miR-146a, which has been demonstrated to be higher in MS lesions. They reported that further functional studies and larger sample sizes are required to corroborate the results of their study and help to unravel the exact mechanisms that these miRNAs have in MS pathophysiology [20].

Wu et al. conducted an investigation in 2015 to examine the role of miR-146a in the pathogenesis of MS, involving six MS patients and six healthy controls. Examining the expression level of miR-146a in the human brain microvessels of MS lesions was the primary objective of their investigation, with a focus on its possible involvement in blood–brain barrier dysfunction in the pathophysiology of MS. Their analysis showed that cerebral microvascular expression of miR-146a was elevated around 1.5-fold in active MS brain lesions compared with that in normal white matter [21].

Martin et al. (2020) examined the expression profile of miR-146a in eight human progressive white matter (WM) brain tissue samples from eight active lesions (AL) in MS patients as well as eight non-active white matter (NAWM) areas. They contrasted these with eight WM samples from healthy individuals who had non-neurological diseases. They quantified the expression level of miR-146a using the qPCR technique, and they demonstrated that the highest levels of miR-146a expression were found in active lesions [22].

mRNA expression of miR-155 in multiple sclerosis (MS) patients

Balkan et al. conducted a study in 2021 involving 20 healthy controls and 20 RRMS patients. For their analysis, they extracted miRNAs from blood samples of both patients and control groups to examine the level of expression of specific microRNAs. The objective of their investigation was to enhance our knowledge of the underlying mechanisms of MS physiopathology. Relapsing–remitting multiple sclerosis (RRMS) patients had a lower miR-155 level than participants in the control group, according to the researchers' quantitative real-time PCR technique ($p < 0.005$) [23].

A study by Lopez-Ramirez et al. (2014) compared the expression of miR-155 in MS lesions with active demyelination and inflammation to those in MS patients' normal-appearing white matter (NAWM) and in the healthy participant's white matter without neurological diseases. Through the application of the quantitative RT-PCR technique, their investigation, which involved six individuals diagnosed with multiple sclerosis (MS) and six healthy individuals, demonstrated a heightened expression of miR-155 within the neurovascular unit of MS lesions. This expression level was discovered to be significantly higher when compared to the level of expression observed in non-lesional MS white matter (MS-NAWM) and in the white matter of individuals without MS. In their study, they showed the possibility that microRNA-155 contributes to blood–brain barrier breakdown during the neuroinflammation stage by changing the appearance and function of the neurovascular endothelium, hence revealing potential therapeutic targets for the improvement of central nervous system inflammatory disorders [24].

In 2014, Zhang et al. conducted a study in which they used reverse transcription polymerase chain reaction

(RT-PCR) to examine the expression levels of eight extracellular microRNAs, specifically miR-155, obtained from the serum samples of 31 multiple sclerosis (MS) patients, 32 Guillain-Barré syndrome (GBS) patients (as a control group for other neuro-immunological diseases), and 31 healthy participants. The study results demonstrated that MiR-155 showed the most substantial increase (fold change = 3.65; $p < 0.001$). The findings of the study revealed that the expression of miR-155 in the serum of MS patients was substantially higher than that of GBS patients and healthy participants. The study's results indicate that miR-155 is important for the regulation of MS and may be a great target for therapeutic intervention [25].

In order to examine the functional significance of upregulated miR-155 expression in myeloid cells in relation to MS, Moore et al. carried out an experiment in 2013. As compared to individuals without MS, the study's CD14 + cells from untreated relapsing–remitting MS patients had higher expression of both miR-155 ($p = 0.0039$) and miR-146a ($p = 0.0026$) [26].

The expression patterns of a few microRNAs that are involved in inflammatory processes, such as miR-155, and how they change following therapy with dimethyl fumarate were evaluated in another investigation conducted by Giuliani et al. in 2021 on 24 RRMS patients and 21 healthy subjects. Using RT-qPCR to measure microRNA levels in plasma, they demonstrated that healthy control participants had an elevated expression level of miR-146a-5p ($p = 0.041$). According to their results, there was no statistically significant difference in the levels of miR-155 between the MS patients and the control group ($p = 0.854$). The limited sample size of their study was the main constraint, since it prevented their ability to do subgroup analyses based on particular disease characteristics [27].

Elkhodiry et al. (2021) included 10 healthy individuals and 25 patients with relapsing–remitting multiple sclerosis (RRMS) in their research. Evaluating the expression levels of miR-155, ICAM1, ITGB2, perforin, and granzyme B in CD8 + T cells of RRMS patients following different treatment regimens was the primary goal of their study. The investigation also sought to examine the relationship between the genes under investigation and the Expanded Disability Status Scale (EDSS), as well as the expression of miR-155 in the MS patients. Using the real-time polymerase chain reaction (RT-PCR) technique, they evaluated the expression pattern of miR-155, ICAM1, ITGB2, perforin, and granzyme B in CD8 + T cells extracted from peripheral blood samples of patients with relapsing–remitting multiple sclerosis (RRMS) and compared them to those of healthy control individuals. According to their analysis, participants with RRMS had lower levels of miR-155 expression and higher levels of ITGB2, ICAM1, perforin, and granzyme B expression when compared to healthy participants. Furthermore, compared to RRMS patients who were not treated, they found a significant reduction in the expression level of miR-155 in patients who were treated with Fingolimod and Interferon B-1a. According to the author's claim, these results are consistent with the potential value of miR-155 as a prognostic and diagnostic biomarker in the physiopathological pathways of MS [28].

Using a microbead-based approach, Paraboschi et al. examined the role of 22 immune-related miRNAs that were isolated from peripheral blood mononuclear cells of MS patients as well as control individuals. Their study's objective was to examine these putative miRNAs' expression levels and their significance for the etiology and development of MS. After analyzing the expression pattern of miRNAs among the two groups, the results showed that the most upregulated miRNA was miR-155 (fold change = 3.30; $p = 0.013$). They declared that their study had several limitations. First of all, using PBMCs rather than isolated T-cell subtypes may weaken cell-specific features and be impacted by differences in the relative cellular makeup. In addition, the results from their gene expression analysis data should be expanded to larger, more homogeneous cohorts of RR patients in the remitting phase [29].

Another investigation was conducted by Gselman et al. in 2023 on a group of Slovenian patients with relapsing–remitting multiple sclerosis (RRMS). Their study aimed to assess the relationship between the expression of miR-155-5p, supplementation with cholecalciferol, and miR-155-5p targets. Following cholecalciferol supplementation at 1000 IU and 4000 IU, they observed a statistically significant decrease in miR-155 expression in the peripheral blood monolayers of both the case and control groups. Their analysis showed that the expression of miR-155 decreased from 0.0015 ± 0.0015 to 0.0008 ± 0.0008 ($p = 1.53 \times 104$) after receiving 1000 IU of cholecalciferol supplementation. Furthermore, it was discovered that the group supplemented with 4000 IU of cholecalciferol showed a decrease in the expression of miR-155-5p from 0.0013 ± 0.0011 to 0.0004 ($p = 0.021$) [30]. The summary of the results is given in Table 1.

Discussion

Examining advancements in the field of miR-146a and miR-155 research as possible diagnostic and prognostic biomarkers for multiple sclerosis was the objective of this investigation. The criteria for selection of these candidate miRNAs were based on their documented involvement in autoimmunity, inflammation, and innate immunity, as reported in previous literature. Multiple sclerosis is a

Table 1 Summary of reviewed articles

Study	Country	Patients	Controls	miRNA	Biological Material	Technique*	Result
Ashrafi et al. [17]	Iran	75 RRMS patients	75 healthy	miR-155	PBMCs	RT-PCR	Decreased in patients ($p=0.005$)
Shademan et al. [18]	Iran	30 MS patients (PPMS, SPMS, RRMS)	30 healthy	miR-146a, miR-155	Blood samples	RT-PCR	miR-146a and miR-155 increased in MS patients ($p<0.001$)
Mameli et al. [19]	Italy	26 MS patients	26 healthy	miR-155, miR-132	PBMCs	RT-PCR	Increased in 10 out of 24 MS patients
Muñoz-San Martín et al. [20]	Spain	46 MS patients	None	miR-146a	CSF	qPCR	Higher in MS lesions
Wu et al. [21]	China	6 MS patients	6 healthy	miR-146a	Brain micro vessels	RT-PCR	Elevated in active MS brain lesions (around 1.5-fold)
Martin et al. [22]	USA	8 MS patients (AL and NAWM areas)	8 healthy (non-neurological)	miR-146a	WM brain tissue	qPCR	Highest levels in active lesions
Balkan et al. [23]	Turkey	20 RRMS patients	20 healthy	miR-155	Blood samples	qRT-PCR	Decreased in patients ($p<0.005$)
Lopez-Ramirez et al. [24]	Spain	6 MS patients	6 healthy	miR-155	Brain lesions, NAWM	RT-PCR	Heightened in MS lesions compared to non-lesional MS white matter and healthy white matter
Zhang et al. [25]	China	31 MS patients	31 healthy, 32 GBS patients	miR-155	Serum	RT-PCR	Increased in MS patients compared to GBS patients and healthy controls (fold change = 3.65; $p<0.001$)
Moore et al. [26]	USA	Untreated RRMS patients	Individuals without MS	miR-155, miR-146a	CD14 + cells	RT-PCR	Higher expression of miR-155 ($p=0.0039$) and miR-146a ($p=0.0026$) in RRMS patients
Giuliani et al. [27]	Italy	24 RRMS patients	21 healthy	miR-146a-5p, miR-155	Plasma	RT-qPCR	Elevated miR-146a-5p in healthy controls ($p=0.041$). No significant difference in miR-155 ($p=0.854$)
Elkhodiry et al. [28]	Egypt	25 RRMS patients	10 healthy	miR-155	CD8 + T cells	RT-PCR	Decreased in patients. Significant reduction in treated patients
Paraboschi et al. [29]	Italy	MS patients	Control individuals	miR-155	PBMCs	Microbead-based approach	Upregulated (fold change = 3.30; $p=0.013$)
Gselman et al. [30]	Slovenia	Slovenian RRMS patients	Control groups (cholecalciferol study)	miR-155-5p	Peripheral blood mononuclear cells	qRT-PCR	Decreased after cholecalciferol supplementation (1000 IU and 4000 IU)

*" RT-PCR" stands for reverse transcription polymerase chain reaction, "qPCR" stands for quantitative polymerase chain reaction, and "RT-qPCR" stands for reverse transcription quantitative polymerase chain reaction

chronic inflammatory disease that is marked by impairment in the CNS. Research studies have revealed that a majority of individuals affected by MS disease are women, according to epidemiological data [30, 31]. MiRNAs are the most frequent small non-coding RNAs [32]. They are present throughout the body, including the cerebrospinal fluid, plasma, peripheral blood specimens, serum, and interstitial fluid [33]. The expression levels of miRNAs are highly regulated during hematopoiesis and lymphoid cell development. Immune system responses may be compromised by aberrant regulation of particular miRNAs or the overall miRNA network.

Given the highly regulated miRNA-mediated control of immune responses, the expression patterns of miRNAs can serve as indicators of susceptibility to complex diseases [23]. Research has demonstrated the notable impact of microRNAs on a range of physiological processes, including differentiation, growth, development, and metabolism. Owing to their potential to modulate an extensive array of biological processes, there is a prevalent belief that they are critical in various human pathophysiological mechanisms, including inflammation, autoimmunity, and neurodegeneration, all of which are prominent features of multiple sclerosis [34–37]. miRNAs are considered biomarkers in a variety of disorders because of their high stability and RT-PCR detectability. For example, miRNAs may be used for disease screening due to an increasing understanding of their functional roles in cancer [38]. Several investigations have examined the relationship between their expression alterations and disease severity, relapses, and responsiveness to natalizumab medication in total peripheral blood mononuclear cells, T cells, CSF, and serum in MS patients compared to healthy individuals [39]. There has been a growing tendency to employ multiple candidate miRNAs, which are deemed more advantageous than just investigating a singular miRNA, with an emphasis on the potential of microRNAs as biomarkers for early detection and prognosis of different diseases [40–42]. miRNA-155 functions as a modulator of inflammatory processes and contributes to the pathophysiology of MS through multiple mechanisms [39]. Recent studies have indicated that the activation of toll-like receptors in monocytes and dendritic cells leads to the upregulation of the expression of several miRNAs, including miR-146a, miR-155, and miR-21 [43]. Certain miRNAs, including miR-155, show noticeable upregulation during the early phase following stimulation, while other miRNAs exhibit upregulation at successive phases of stimulation. In conjunction with other pathways, these miRNAs play a critical role in modulating inflammatory mechanisms by selectively targeting the messenger RNAs of particular toll-like receptor signaling elements [44]. Through modifying the interaction between brain endothelial cells (BEC) and their surrounding matrix, Lopez-Ramirez et al. asserted that miR-155 operates as a novel inhibitory factor of blood–brain barrier (BBB) function in the context of neuroinflammation. Numerous neuroinflammatory CNS disorders, including multiple MS, are believed to be largely impacted by this process [19]. According to available research, miRNAs may be useful biomarkers for diagnosing and predicting MS in clinical settings. However, the amount of research examining the expression patterns of miRNAs in MS is still quite limited.

Additionally, research exploring the possibility of utilizing microRNAs as biomarkers for disease prognosis and diagnosis is still in its early stages. Because of this, the results of these studies frequently lack consistency and replicability.

Investigations evaluating miRNAs often face several constraints, including the use of a wide range of biological samples and different methodologies for miRNA isolation and analysis (e.g., microarray, qRT-PCR, dPCR, and RNA sequencing). Existing research has indicated variances in the patterns of miRNA expression between various cell types within each MS subtype when compared to the control group. Thorough investigations on the potential of miRNA expression levels in cells as a distinguishing marker for different MS subtypes are still lacking. In addition, the limited size of the sample and the reproducibility of findings in independent cohorts are noticeable limitations.

Our review showed that out of six articles that investigated the expression level of miR-146a, five of them reported that its expression was elevated in MS patients compared with healthy controls [18, 21, 23, 24, 27], and in only one article, the expression level of miR-146a was upregulated in controls compared with patients [22].Of the 11 articles that assessed the expression level of miR-155, six reported that its expression level was elevated in patients in comparison with healthy controls [18–21, 26, 28]. In three studies, the expression level of miR-155 was decreased in patients compared with controls [17, 23, 25], and in one study, there was no statistically significant difference in the expression level of miR-155 in both groups [22]. In one study that investigated the role of cholecalciferol supplementation on miR-155 expression, it was shown that its expression decreased statistically significantly [29]. The trends in both miRNAs's expression patterns indicate that they may be suitable biomarkers for the prognostic and diagnostic purposes of MS. The inconsistency that is shown in the miR-155 expression in different studies between cases and controls may be due to the use of different sample sizes and ages of the

study subjects, different geographical locations, or the use of different samples such as PBMCs, serum, or CSF for the study.

Conclusion

Our systematic review highlights the critical role of microRNAs, particularly miR-155 and miR-146a, in the pathogenesis of multiple sclerosis (MS). We have elucidated the association between aberrations in the expression and function of these microRNAs and the development of MS, underscoring their potential as promising biomarkers for both the prognosis and diagnosis of the disease. However, to fully leverage their diagnostic and prognostic utility, further research is needed to investigate the correlation between mRNA levels of miR-146a and miR-155 and their corresponding protein expression in MS patients. Understanding this relationship could provide valuable mechanistic insights into MS pathogenesis and facilitate the development of more effective diagnostic and therapeutic strategies. Moreover, the scarcity of reliable biomarkers to differentiate MS subtypes remains a significant challenge. Our review suggests that microRNAs, owing to their presence in various bodily fluids, including peripheral blood samples, serum, cerebrospinal fluid, and extracellular vesicles, hold promise as non-invasive biomarkers for disease prognosis and diagnosis. By harnessing the potential of microRNAs, researchers can pave the way for the development of innovative diagnostic and therapeutic approaches to better manage MS and improve patient outcomes.

Abbreviations

miRNAs	MicroRNAs
MS	Multiple sclerosis
PBMCs	Peripheral blood monocellular cells
PPMS	Primary progressive multiple sclerosis
NAWM	Normal-appearing white matter
RRMS	Relapsing–remitting multiple sclerosis
BEC	Brain endothelial cell
RT-PCR	Real-time polymerase chain reaction
SPMS	Secondary progressive multiple sclerosis
EDSS	Expanded disability status scale
WM	White matter
CNS	Central nervous system
CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
AL	Active lesions

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References

1. Pietrasik S, Dziedzic A, Miller E, Starosta M, Saluk-Bijak J (2021) Circulating miRNAs as potential biomarkers distinguishing relapsing-remitting from secondary progressive multiple sclerosis: a review. Int J Mol Sci 22(21) (2021)
2. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O (2018) Multiple sclerosis. Lancet 391(10130):1622–1636
3. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, Robertson N, La Rocca N, Uitdehaag B, van der Mei I et al (2020) Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. Mult Scler 26(14):1816–1821
4. Miclea A, Salmen A, Zoehner G, Diem L, Kamm CP, Chaloulos-Iakovidis P, Miclea M, Briner M, Kilidireas K, Stefanis L et al (2019) Age-dependent variation of female preponderance across different phenotypes of multiple sclerosis: a retrospective cross-sectional study. CNS Neurosci Ther 25(4):527–531
5. Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, Ebers GC (2006) Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 5(11):932–936
6. Collaborators GBDMS: Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18(3):269–285 (2019)
7. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, Robertson N, La Rocca N, Uitdehaag B, van Der Mei I, Wallin M (2020) Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS. Mult Scler J 26(14):1816–1821
8. Housley WJ, Pitt D, Hafler DA (2015) Biomarkers in multiple sclerosis. Clin Immunol 161(1):51–58
9. Zhou Z, Xiong H, Xie F, Wu Z, Feng Y (2020) A meta-analytic review of the value of miRNA for multiple sclerosis diagnosis. Front Neurol 11:132
10. Gao Y, Han D, Feng J (2021) MicroRNA in multiple sclerosis. Clin Chim Acta 516:92–99
11. Jonas S, Izaurralde E (2015) Towards a molecular understanding of microRNA-mediated gene silencing. Nat Rev Genet 16(7):421–433
12. Kozomara A, Griffiths-Jones S (2014) miRBase: annotating high confidence microRNAs using deep sequencing data. Nucleic Acids Res 42(Database issue):D68–73
13. Zhang K, Wang YW, Wang YY, Song Y, Zhu J, Si PC, Ma R (2017) Identification of microRNA biomarkers in the blood of breast cancer patients based on microRNA profiling. Gene 619:10–20

14. Barwari T, Joshi A, Mayr M (2016) MicroRNAs in cardiovascular disease. J Am Coll Cardiol 68(23):2577–2584
15. Long H, Wang X, Chen Y, Wang L, Zhao M, Lu Q (2018) Dysregulation of microRNAs in autoimmune diseases: pathogenesis, biomarkers and potential therapeutic targets. Cancer Lett 428:90–103
16. Mortazavi-Jahromi SS, Aslani M, Mirshafiey A (2020) A comprehensive review on miR-146a molecular mechanisms in a wide spectrum of immune and non-immune inflammatory diseases. Immunol Lett 227:8–27
17. Ali Ashrafi S, Asadi M, Shanehbandi D, Sadigh Eteghad S, Fazlollahi A, Nejadghaderi SA, Shaafi S (2022) Association between miRNA-145 and miRNA-155 expression in peripheral blood mononuclear cells of patients with multiple sclerosis: a case-control study. BMC Neurol 22(1):405
18. Shademan B, Nourazarian A, Nikanfar M, Biray Avci C, Hasanpour M, Isazadeh A (2020) Investigation of the miRNA146a and miRNA155 gene expression levels in patients with multiple sclerosis. J Clin Neurosci 78:189–193
19. Mameli G, Arru G, Caggiu E, Niegowska M, Leoni S, Madeddu G, Babudieri S, Sechi GP, Sechi LA (2016) Natalizumab therapy modulates miR-155, miR-26a and proinflammatory cytokine expression in MS patients. PLoS ONE 11(6):e0157153
20. Munoz-San Martin M, Reverter G, Robles-Cedeno R, Buxo M, Ortega FJ, Gomez I, Tomas-Roig J, Celarain N, Villar LM, Perkal H et al (2019) Analysis of miRNA signatures in CSF identifies upregulation of miR-21 and miR-146a/b in patients with multiple sclerosis and active lesions. J Neuroinflammation 16(1):220
21. Wu D, Cerutti C, Lopez-Ramirez MA, Pryce G, King-Robson J, Simpson JE, van der Pol SM, Hirst MC, de Vries HE, Sharrack B et al (2015) Brain endothelial miR-146a negatively modulates T-cell adhesion through repressing multiple targets to inhibit NF-kappaB activation. J Cereb Blood Flow Metab 35(3):412–423
22. Martin NA, Hyrlov KH, Elkjaer ML, Thygesen EK, Wlodarczyk A, Elbaek KJ, Aboo C, Okarmus J, Benedikz E, Reynolds R et al (2020) Absence of miRNA-146a differentially alters microglia function and proteome. Front Immunol 11:1110
23. Balkan E, Bilge N (2021) Expression levels of IL-17/IL-23 cytokine-targeting microRNAs 20, 21, 26, 155, and Let-7 in patients with relapsing-remitting multiple sclerosis. Neurol Res 43(9):778–783
24. Lopez-Ramirez MA, Wu D, Pryce G, Simpson JE, Reijerkerk A, King-Robson J, Kay O, de Vries HE, Hirst MC, Sharrack B et al (2014) MicroRNA-155 negatively affects blood-brain barrier function during neuroinflammation. FASEB J 28(6):2551–2565
25. Zhang J, Cheng Y, Cui W, Li M, Li B, Guo L (2014) MicroRNA-155 modulates Th1 and Th17 cell differentiation and is associated with multiple sclerosis and experimental autoimmune encephalomyelitis. J Neuroimmunol 266(1–2):56–63
26. Moore CS, Rao VT, Durafourt BA, Bedell BJ, Ludwin SK, Bar-Or A, Antel JP (2013) miR-155 as a multiple sclerosis-relevant regulator of myeloid cell polarization. Ann Neurol 74(5):709–720
27. Giuliani A, Lattanzi S, Ramini D, Graciotti L, Danni MC, Procopio AD, Silvestrini M, Olivieri F, Sabbatinelli J (2021) Potential prognostic value of circulating inflamma-miR-146a-5p and miR-125a-5p in relapsing-remitting multiple sclerosis. Mult Scler Relat Disord 54:103126
28. Elkhodiry AA, Zamzam DA, El Tayebi HM (2021) miR-155 and functional proteins of CD8+ T cells as potential prognostic biomarkers for relapsing-remitting multiple sclerosis. Mult Scler Relat Disord 53:103078
29. Paraboschi EM, Solda G, Gemmati D, Orioli E, Zeri G, Benedetti MD, Salviati A, Barizzone N, Leone M, Duga S et al (2011) Genetic association and altered gene expression of mir-155 in multiple sclerosis patients. Int J Mol Sci 12(12):8695–8712
30. Gselman S, Fabjan TH, Bizjak A, Potocnik U, Gorenjak M (2023) Cholecalciferol supplementation induced up-regulation of SARAF gene and down-regulated miR-155-5p expression in slovenian patients with multiple sclerosis. Genes (Basel) 14(6)
31. Amur S, Parekh A, Mummaneni P (2012) Sex differences and genomics in autoimmune diseases. J Autoimmun 38(2–3):J254–J265
32. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T (2001) Identification of novel genes coding for small expressed RNAs. Science 294(5543):853–858
33. He L, Hannon GJ (2004) MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 5(7):522–531
34. Mendell JT, Olson EN (2012) MicroRNAs in stress signaling and human disease. Cell 148(6):1172–1187
35. Ardekani AM, Naeini MM (2010) The role of microRNAs in human diseases. Avicenna J Med Biotechnol 2(4):161
36. Li Y, Kowdley KV (2012) MicroRNAs in common human diseases. Genom Proteom Bioinf 10(5):246–253
37. Sheinerman KS, Toledo JB, Tsivinsky VG, Irwin D, Grossman M, Weintraub D, Hurtig HI, Chen-Plotkin A, Wolk DA, McCluskey LF et al (2017) Circulating brain-enriched microRNAs as novel biomarkers for detection and differentiation of neurodegenerative diseases. Alzheimers Res Ther 9(1):89
38. Rupaimoole R, Slack FJ (2017) MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov 16(3):203–222
39. Maciak K, Dziedzic A, Miller E, Saluk-Bijak J (2021) miR-155 as an important regulator of multiple sclerosis pathogenesis: a review. Int J Mol Sci 22(9)
40. Zou X, Wei J, Huang Z, Zhou X, Lu Z, Zhu W, Miao Y (2019) Identification of a six-miRNA panel in serum benefiting pancreatic cancer diagnosis. Cancer Med 8(6):2810–2822
41. Yan L, Zhao W, Yu H, Wang Y, Liu Y, Xie C (2016) A comprehensive meta-analysis of MicroRNAs for predicting colorectal cancer. Medicine (Baltimore) 95(9):e2738
42. Pogribny IP (2018) MicroRNAs as biomarkers for clinical studies. Exp Biol Med (Maywood) 243(3):283–290
43. Baulina NM, Kulakova OG, Favorova OO (2016) MicroRNAs: the role in autoimmune inflammation. Acta Naturae 8(1(28)):21–33
44. Junger WG (2011) Immune cell regulation by autocrine purinergic signalling. Nat Rev Immunol 11(3):201–212

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