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Original article

Decoding disease burden in multiple sclerosis: The role of IL-10 as biomarker of neuroinflammation and neurodegeneration

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic neuroinflammatory disease with heterogeneous clinical presentations and progression rates that pose challenges to its management. Identifying prognostic biomarkers is crucial for individualized treatment approaches. Interleukin-10 (IL-10) has emerged as a key anti-inflammatory cytokine with neuroprotective effects, while Chitinase-3-like protein 1 (CHI3L1) reflects the pathogenic glial activation and neurodegeneration.

Objective: This study aimed to assess baseline serum IL-10 and CHI3L1 levels as biomarkers of disease burden and their correlation with clinical, cognitive, and quality-of-life (QoL) parameters in disease-modifying therapy (DMT)-naïve MS patients.

Methods: A cross-sectional, case-control study was conducted on 115 DMT-naïve MS patients and 15 healthy controls. Only 73 RRMS and 29 CIS confirmed MS participated in the study analysis. Serum IL-10 and CHI3L1 levels were measured using sandwich ELISA kits and were correlated with various demographic, clinical, motor, cognitive, and quality of life (QOL) parameters.

Results: Serum levels of IL-10 and CHI3L1 were significantly higher among MS patients compared to the healthy controls ($P = 0.0001$ for each one) and were negatively correlated with each other ($r = -0.529$ and $P < 0.001$). Second finding IL-10 levels negatively correlated with duration of disease ($r = -0.389$, $P < 0.001$), total number of relapse ($r = -0.445$, $P < 0.001$), motor disability (EDSS), Timed 25-Foot walk test (25-FWT), and depression scores ($r = -0.398$, $P = 0.003$, $r = -0.340$, $P = 0.002$ and $r = -0.288$, $P = 0.008$ respectively). It's positively correlated with most domains of QoL. CHI3L1 correlated positively with the total number of relapses ($r = 0.253$, $P = 0.021$), and EDSS ($r = 0.346$, $P = 0.001$), while negatively correlated with vitality, social, physical function, and general health domains of QoL ($P = 0.009$, 0.03, 0.001, and 0.013, respectively)

Conclusion: IL-10 serves as a potential biomarker for disease burden in MS, with protective effects on QoL, highlighting its role in the early identification of favorable disease profiles and personalized disease management.

1. Introduction

MS is a complex neuroinflammatory disorder characterized by the activation of immune responses leading to demyelination and neurodegeneration (Giovannoni et al., 2022). The clinical heterogeneity of MS has long posed challenges to its management (Engelhardt et al., 2022). Some patients may experience few relapses, complete recovery, and maintain a good level of function over time referred to as "benign MS", while others may experience a more rapid accumulation of disabilities, referred to as "aggressive or highly active MS" (Correale et al., 2023). Why a patient may experience such varying rates of disability accumulation and disease progression remains a topic of ongoing research that involves a complex interplay of genetic, environmental, and clinical factors (Oh et al., 2024). Understanding the molecular and cellular

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mechanisms underlying MS is critical for identifying biomarkers that can elucidate disease pathways and aid in personalized therapeutic strategies (Oh et al., 2024). Among the emerging biomarkers, interleukin-10 (IL-10) has garnered attention for its dual role in modulating neuroinflammation and neurodegeneration (Gilio et al., 2024). Elevated levels of IL-10 were associated with reduced disease activity, while lower levels were associated with more tissue damage as shown in IL-10-deficient mice exhibiting more severe EAE (Lobo-Silva et al., 2016). IL-10 is a pleiotropic cytokine predominantly secreted by regulatory T cells (Tregs), B cells, and macrophages. It exerts potent anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) (Vani, 2022). In the CNS, IL-10 shifts microglia towards an anti-inflammatory, reparative phenotype (M2 polarization). This polarization promotes remyelination and neuronal survival through enhanced BBB integrity, clearance of myelin debris, and secretion of neurotrophic factors (Guo et al., 2022). Beyond its anti-inflammatory effects, IL-10's interaction with microglia significantly influences synaptic transmission, pruning, and plasticity, crucial for maintaining CNS health, emphasizing the broader neuroprotective role of IL-10 against cognitive and functional impairments commonly observed in MS patients (Colonna and Butovsky, 2017).

The heterogeneity in MS presentations, disease outcomes, and responses to DMTs may be partially explained by inter-individual differences in IL-10 production and signaling. Genetic variations in the IL-10 receptor, such as the S138G loss-of-function polymorphism, have been associated with increased susceptibility to MS (Ben Fredj et al., 2017). Environmental factors, including intestinal microbes, can modulate the IL-10/IL-10R axis, suggesting that lifestyle and environmental interventions could influence MS progression through effects on IL-10 signaling (Eryn et al., 2023).

On the other hand, Chitinase-3-like protein-1 (CHI3L1) is considered a marker of ongoing microglial activation and neuroinflammation, although it is also produced by other cell types, including astrocytes (Jatczak-Pawlik et al., 2024).

In this context, this study aimed at the identification of baseline serum IL-10 as a protective biomarker before interaction with any DMTs and the state of microglial activation reflected by CHI3L1 levels, and their correlation with various demographic, clinical, cognitive, and quality of life (QoL) parameters in DMT-naïve MS patients.

2. Patients and methods

2.1. Study design and setting

This was a cross-sectional, case-control study conducted at Al-Eman MS Center in Assiut, Egypt, between January 2023 and June 2024.

2.2. Study Population

One hundred and fifty DMT-naive MS patients were enrolled consecutively during the study period, 115 patients and 15 Healthy controls (HCs) were recruited according to the following inclusion and exclusion criteria:

Inclusion Criteria: DMT-naïve MS patients: Diagnosed with MS based on the 2017 McDonald Criteria (Thompson et al., 2018), no prior or current use of disease-modifying therapies (DMTs), and aged between 18 and 60 years. All included patients were in a clinically stable phase and had not experienced a relapse within at least three months before blood sampling.

Clinically isolated syndrome (CIS) is diagnosed with MS if the first MRI study meets criteria for dissemination in space (DIS) and dissemination in time (DIT), or if OCB are detected, which may replace a clinical event or DIT in the MRI study (Carroll, 2018).

All relapsing remitting multiple sclerosis (RRMS) and CIS-MS patients were included, while Naïve patients diagnosed with progressive MS (primary or secondary progressive MS) were excluded.

To minimize disease heterogeneity and focus on the most common phenotype, the primary statistical analyses were conducted exclusively on RRMS patients (n=73) and patients with CIS (n=29) confirmed MS. Data from patients with SPMS (n=8) and PPMS (n=5) were excluded from the main analyses (Fig. 1: Flowchart).

2.3. Exclusion criteria

Participants were excluded if: An alternative diagnosis was confirmed (e.g., neuromyelitis optica spectrum disorder), or they received corticosteroids or immunosuppressive therapy within the last 3 months. Pregnant or lactating patients or patients who had coexisting neurological or systemic disorders (e.g., epileptic seizures, diabetes mellitus, and hypertension) or had concomitant use of chronic medications for any purpose were also excluded.

Healthy Controls (HCs): Age- and sex-matched individuals without any neurological or systemic illnesses and had no family history of MS or other autoimmune diseases.

3. Methodology

3.1. Clinical, radiological, and laboratory assessments

Each patient was interviewed for demographic data (age, sex, and the number of educational years) and clinical Data including disease duration, number of relapses, and MS phenotypes (clinically isolated syndrome "CIS", relapsing-remitting MS "RRMS", secondary progressive MS "SPMS", and primary progressive MS "PPMS").

3.2. Clinical rating scales

Physical performance was evaluated using the Expanded Disability Status Scale [EDSS] (Kurtzke, 1983), the Nine-Hole Peg Test (9-HPT) to evaluate upper extremity function and dexterity (Mathiowetz et al., 1985), and the timed 25-Foot Walk Test (T25-FW) to assess gait speed and lower extremity function (Goldman et al., 2013).

Cognitive performance was evaluated using the Arabic version of the Brief International Cognitive Assessment for MS (BICAMS) to assess information processing speed, verbal memory, and visuospatial memory using the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT), and Brief Visuospatial Memory Test-Revised (BVMT-R), respectively (Farghaly et al., 2021).

Depression was assessed using the Hamilton Depression Scale (HDRS) (Hamilton, 1960) consisting of 17 items, covering symptoms such as mood, guilt, insomnia, agitation, anxiety, weight loss, and somatic symptoms. Each symptom is scored based on severity, ranging from 0 (absent) to 2, 3, or 4, depending on the item. Participants are evaluated based on their experiences over the past week. Total scores range from 0 to 52, with higher scores indicating more severe depression

Quality of Life (QoL) was assessed using the Short Form Health Survey (SF-36) (Ware and Sherbourne 1992): Participants complete a standardized questionnaire consisting of 36 items, divided into eight domains: 1) Physical Functioning evaluates limitations in performing physical activities such as walking, lifting, and climbing stairs. 2) Vitality: Assesses energy levels and fatigue. 3) Social Functioning: Examines the impact of health on social activities and relationships. 4) Pain: Measures the intensity of pain and its impact on daily activities. 5) General Health Perceptions: Provides an overall evaluation of health status. 6) Emotional well-being. 7) Role limitations due to physical health, and 8) role limitations due to emotional problems. Each domain is scored on a scale of 0 to 100, where higher scores indicate better health status.

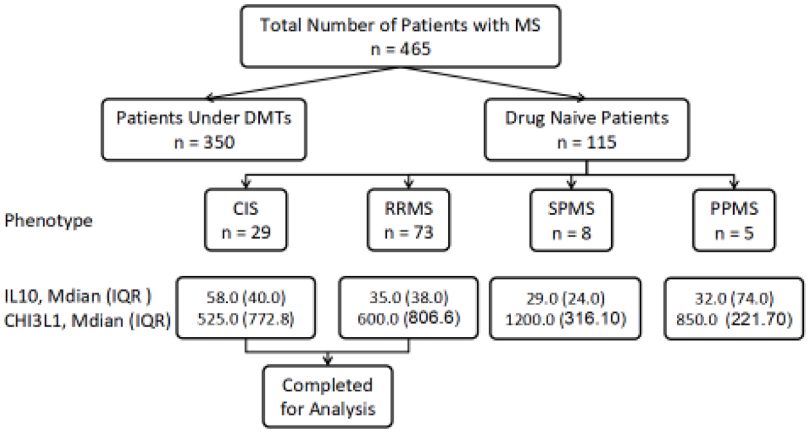

Fig. 1. Shows the flowchart of studied patients: This flowchart shows how 465 MS patients were divided into two groups: those receiving treatment (DMTs) and those who were drug-naive. The drug-naive group (n = 115) was further divided based on MS type: CIS, RRMS, SPMS, and PPMS. For each type, average levels in pg/mL of two serum markers— interleukin-10 (IL-10) and chitinase-3-like protein 1 (CHI3L1)—are reported. IL-10 levels are highest in CIS and decrease as the disease becomes more advanced, with the lowest levels seen in PPMS. On the other hand, CHI3L1 levels tend to increase in the more progressive form SPMS. These patterns highlight the potential of IL-10 and CHI3L1 as differential biomarkers in monitoring disease stage and inflammatory status in drug-naive MS patients.

3.3. Measurement of IL-10 and CHI3L1

Serum levels of IL-10 and CHI3L1, also known as YKL-40 or GP39 were measured using quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits (DLdevelop, China; IL-10: Catalog No. DL-IL10-Hu, CHI3L1: Catalog No. DL-GP39-Hu), according to the manufacturer's protocols. Blood samples were obtained during remission to avoid confounding effects of acute inflammation on cytokine levels, with no evidence of other autoimmune, infectious, or systemic diseases. Blood samples were collected, allowed to clot at room temperature for 2 hours, and centrifuged at 1000 × g for 20 min. The resulting serum was aliquoted and stored at −80° until analysis. All samples were brought to room temperature before testing and analyzed in duplicate. Standard curves were generated using a series of two-fold dilutions ranging from 31.2 pg/mL to 2000 pg/mL. Sample concentrations were calculated based on the standard curve, and values were adjusted for any dilution factors. The minimum detectable concentrations were <11.3 pg/mL for IL-10 and <12.2 pg/mL for CHI3L1. Intra-assay and inter-assay coefficients of variation were <10 % and <12 %, respectively, for both biomarkers, indicating good reproducibility.

3.3.1. Statistical analysis

Data were analyzed using SPSS version 26. Continuous non-parametric variables were expressed as medians and interquartile ranges (IQRs), while categorical data were presented as frequencies and percentages. Group comparisons were conducted using the Mann-Whitney U test for continuous non-parametric variables and the Chi-square test for categorical variables. Spearman's rank correlation coefficient was used to assess relationships between biomarker levels (IL-10, CHI3L1) and clinical, motor, cognitive, depression, and QoL parameters. P-values below 0.05 were considered statistically significant.

3.3.2. Ethical approval

The study adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of the Faculty of Medicine at Assiut University, Assiut, Egypt (IRB local approval number: 17300883). A written informed consent was obtained from all participants before enrollment.

4. Results

Demographic, clinical, and laboratory data of the studied cohort are shown in (**Demographic,** clinical, and laboratory data of the studied cohort) (Table 1). Serum levels of IL-10 and CHI3L1 were significantly elevated in DMT-naive MS patients compared to age, sex, and education-matched HCs ($P < 0.001$), indicating these biomarkers have a potential role in MS pathology

Fig. 2 shows the correlation between serum level of IL-10 and CHI3L1 among drug naive MS patients (115). A moderate negative correlation was observed between IL-10 and CHI3L1 levels (Rs = −0529, $P < 0.001$), assessed exclusively in MS patients. This finding suggests an inverse relationship between anti-inflammatory and pro-inflammatory processes within the same cohort, suggesting an inverse association between the anti-inflammatory and neuroprotective effects of IL-10 and CHI3L1, the marker of pathogenic microglial activation in MS.

Demographic, clinical, and laboratory data of the studied cohort are shown in Table 1.

As shown in Tables 2 and 3, higher IL-10 levels were associated with improved clinical and quality of life (QoL) measures. Specifically, IL-10

Table 1
Demographic, clinical, and laboratory data of the studied cohort of DMT-Naïve MS patients.

	Total MS patients (n= 102)	Control (n= 15)	*P*-value
IL 10, median (IQR)	45.0 (40.0)	20.8 (12.0)	**<0.001** *
CHI3L1, median (IQR)	600.0 (774.8)	38.4 (37.7)	**<0.001** *
Age, median (IQR)	30.0 (15.0)	31.5 (11.8)	0.958
Sex, n (%)			0.950
Females	76.0 (74.5)	11.0 (73.3)	
Males	26.0 (25.5)	4.0 (26.7)	
Disease duration in years, median (IQR)	1.0 (2.8)	NA	–
Total number of relapses, median (IQR)	2.0 (2.0)	NA	–
EDSS, median (IQR)	1.5 (1.0)	NA	–
MS phenotype, n (%)		NA	–
CIS	29.0 (28.4)		
RRMS	73.0 (71.6)		

CIS: Clinically Isolated Syndrome; EDSS: Expanded Disability Status Scale; IQR: Interquartile Range; MS: Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis

* = *P* value was set significantly below 0.05

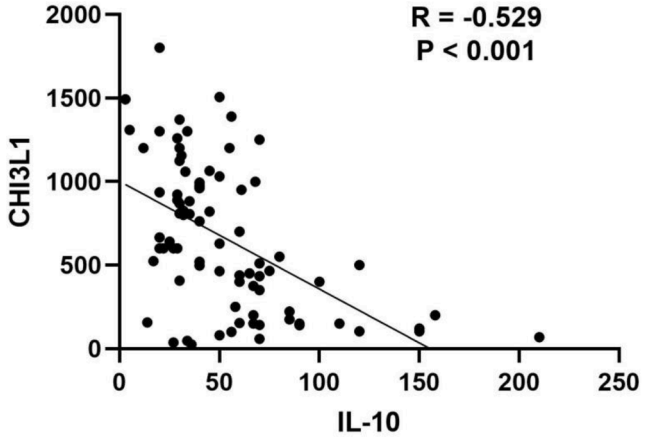

Fig. 2. Scatter plot showing the negative correlation between serum IL-10 and CHI3L1 levels in MS patients (n=115). The black trendline indicates a moderate inverse correlation (Spearman Rs = −0.450, $P < 0.001$).

Table 2
Correlation between IL-10 and CHI3L1 levels with demographic, and clinical rating scales among drug naïve MS patients (102 patients: 73 RRMS and 29 CIS-MS).

	IL-10 levels		CHI3L1 levels	
	Correlation coefficient (Rs)	P-value	Correlation coefficient (Rs)	*P*-value
Age	0.038	0.730	0.181	0.101
Disease duration in years	−0.389**	**<0.001***	−0.046	0.680
Total number of relapses	−0.445**	**<0.001***	0.253	**0.021***
EDSS score	−0.398**	**<0.001***	0.346*	**<0.001***
9-hole pig test	−0.113	0.325	0.053	0.645
25-foot walk test	−0.340**	**0.002***	0.199	0.073

EDSS: Expanded Disability Status Scale
* = *P* value was set significantly below 0.05

inversely correlated with total number of relapses ($P < 0.001$), disease duration ($P < 0.001$), motor impairment measured by the EDSS ($P < 0.001$) (Fig. 3), and 25-FWT ($P = 0.002$), as well as negatively correlated with HDRS score ($P = 0.008$) (Fig. 4), indicating that elevated IL-10 could reduce disease burden and depression. A positive correlation was found with multiple QoL domains, including physical function (P = 0.004), vitality ($P < 0.001$), emotional well-being ($P = 047$), social functioning (P = 0.015), and general health ($P < 0.001$). No significant correlations could be observed between both IL-10 and cognitive performance in subtests of the BICAMS. These findings suggest that IL-10 may confer neuroprotective effects, enhance cognitive resilience, and improve overall well-being and quality of life in MS patients.

Conversely, CHI3L1 demonstrated weaker correlations with clinical parameters. Positive correlations emerged only with total number of relapses (P = 0.021) and EDSS score ($P = 0.001$), highlighting CHI3L1's potential role in chronic neuroinflammation as MS progresses. However, CHI3L1 did not significantly correlate with cognitive performance and had a limited impact on QoL, with only Physical function ($P = 0.001$), vitality ($P = 0.009$), social functioning ($P = 0.030$), and general health ($P = 0.013$) negatively affected.

5. Discussion

This study emphasizes the anti-inflammatory and neuroprotective role of IL-10, in the pathophysiology of MS. The main finding of the present study, first: Serum levels of IL-10 and CHI3L1 were significantly higher among MS patients compared to the healthy controls and were negatively correlated with each other ($P < 0.001$). Second, IL-10 levels negatively correlated with disease duration, total number of relapses, EDSS, 25-FWT, and depression scores ($P = < 0.001, < 0.001, < 0.001$, and 0.008, respectively). It's positively correlated with most domains of QoL. CHI3L1 correlated positively with the total number of relapses ($P = 0.021$) and EDSS ($P < 0.001$) and had a negative correlation with Vitality, social functioning, physical functioning, and general health domains of QoL (P = 0.009, 0.030, 0.001, and 0.013, respectively).

Table 3
Correlation between IL-10 and CHI3L1 levels and cognitive performance, depression, and different domains of Quality of Life among drug Naïve MS patients (102 patients: 73 RRMS and 29 CIS-MS).

	IL 10 level		CHI3L1	
	Correlation coefficient (Rs)	P-value	Correlation coefficient (Rs)	*P*-value
Cognition (BICAMS)				
SDMT	0.060	0.612	−0.190	0.109
CVLT	−0.039	0.723	.026	0.816
BVMT-R 1	0.186	0.101	−0.109	0.340
Depression (Hamilton-D)	**−0.288****	**0.008***	0.168	0.132
Quality of life (SF36)				
Physical function	0.358**	**0.004***	−0.408**	**0.001***
limitation physical	0.241	0.055	−0.227	0.073
limitation emotional	0.305*	0.014	−0.201	0.115
Vitality	0.462**	**<0.001***	−0.328**	**0.009***
Emotional well being	0.249*	**0.047***	−.0174	0.172
Social	0.302*	**0.015***	−0.274*	**0.030***
Pain	0.281*	**0.024***	−0.247	0.051
General Health	0.454**	**<0.001***	−0.311*	**0.013***

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT: California Verbal Learning Test; SDMT: Symbol Digit Modalities Test
* = *P* value was set significantly below 0.05

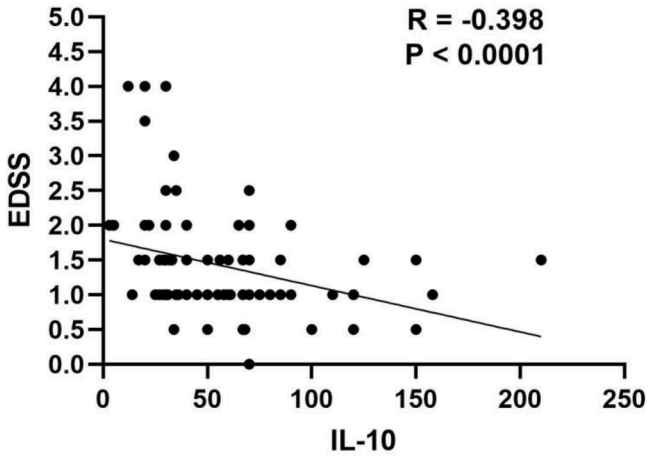

Fig. 3. Correlation of IL-10 levels with disability scale (EDSS) among RRMS and CIS-MS patients (n=102). Higher IL-10 is associated with lesser disability (Spearman Rs = −0.398, $P < 0.001$).

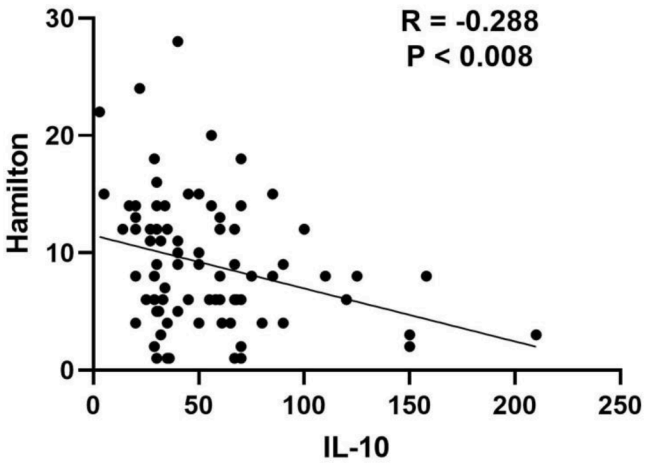

Fig. 4. Negative correlation between IL-10 levels and Hamilton Depression Scale scores among RRMS and CIS-MS patients (n=102), (Spearman Rs = −0.280, $P = 0.008$), highlighting the potential mood-stabilizing role of IL-10.

5.1. Neuroinflammatory and neuroprotective of IL-10

Higher serum levels of IL-10 were found in DMT-naive MS patients compared to HCs ($P < 0.0001$), which could reflect a compensatory response to the inflammatory processes in MS. A significant increase in the concentrations of several proinflammatory and anti-inflammatory cytokines, including IL-10 in patients with MS compared to HCs were reported by others (Gilio et al., 2024). This elevation was also observed in the secondary progressive phase of MS compared to HCs (Kallaur et al., 2017). Elevated IL-10 levels were also reported in other autoimmune disorders like systemic lupus erythematosus (Abd Elazeem et al., 2018). In the present study, the higher serum IL-10 levels were significantly associated with reduced disease activity.

Serum IL-10 levels were inversely correlated with the number of reported relapses and duration of disease, which were consistent with the previous finding by Wei et al. (2019), where lower IL-10 levels were associated with shorter times to the second relapse, conversion of CIS to MS, and subsequent higher relapse rates (Wei et al., 2019). The increase of IL-10 levels in RRMS-treated patients with interferon-beta 1a, which increases IL-10-secreting cells, was associated with a favorable response to treatment in the form of reduced relapse frequency, suggesting that IL-10 could serve as a biomarker for treatment efficacy and relapse risk (Pietro Biagio et al., 2008, Rodica et al., 2017). Photobiomodulation therapy has been shown to increase IL-10 levels in RRMS patients with a consequent reduction in relapse frequency (Miguel Angel et al., 2022, Tamiris et al., 2020). Another Egyptian study investigated the dynamic changes in IL-10 levels during and after relapse and found a statistically significant decrease in serum IL-10 in RRMS patients during relapse compared with the remission phase, emphasizing the anti-inflammatory role of IL-10 (Tawfik et al., 2016). By reducing inflammation, IL-10 exerts direct neuroprotective effects through modulating synaptic transmission and maintaining the balance between excitatory and inhibitory signals in the brain (Gilio et al., 2024).

5.2. Association of IL-10 with motor disability and cognitive outcomes

Lower serum IL-10 levels were correlated with worse performance on EDSS ($r = −0.398$, $P < 0.0001$) and 25-FWT ($r = −0.340$, $P = 0.002$), but no correlation was found with upper limb function (9-HPT). Kallaur et al. (2017) compared the cytokine profile between RRMS patients and patients with progressive disease and found an inverse correlation of serum IL-10 with EDSS score in only progressive MS but not RRMS, indicating that higher IL-10 levels may be associated with reduced disease progression and motoric disability (Kallaur et al., 2017). The difference in results of the current study from the previously mentioned study could be attributed to different patient profiles, as in the current study, most patients were in the early stages of the disease. Also, Boxel-Dezaire et al. (1999) found that, particularly in SPMS patients, decreased expression of IL-10 was associated with increased disease activity and progression (van Boxel-Dezaire et al., 1999). Lower IL-10 associated with higher disability of SPMS patients (Petereit et al., 2003), while Fissolo et al. (2024) found that serum IL-10 levels predict disability progression in patients with PPMS (Fissolo et al., 2024). The present study supports the previous results as IL-10 levels are highest in CIS and decrease as the disease becomes more advanced, with the lowest levels seen in PPMS. On the other hand, CHI3L1 levels tend to increase in the more progressive form SPMS (Kim, 2023). These patterns highlight the potential of IL-10 and CHI3L1 as differential biomarkers in monitoring disease stage and inflammatory status in drug-naive MS patients. However, because of the small number of patients with progressive MS, they were excluded from the final analysis.

Regarding cognitive performance, we failed to find a significant correlation between it and IL-10, which may be related to the relatively small sample size. This finding was in contrast to other studies, for instance, Ward et al. (2023) found that higher IL-10 levels were associated with better visual memory scores (Ward et al., 2023). Keegan et al. (2023) have linked lower IL-10 levels in healthy older adults who are carriers of the IL10 AA genotype with impaired processing speed and executive function, emphasizing the role of IL-10 as a possible resilience factor (Keegan et al., 2024).

5.3. Association of IL-10 with depression and QoL outcomes

Since depression is increasingly recognized as an inflammatory condition and a common comorbidity in MS, serum IL-10 levels were correlated negatively with depression scores on the HDRS. Pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β are frequently elevated in both depression and MS, suggesting a shared inflammatory pathway (Kiropoulos et al., 2025). A study by Newland et al. (2022) found that salivary IL-10 levels were significantly negatively associated with depression in veterans with MS (Newland et al., 2022). In experimental models, IL-10 administration has been shown to rescue depression-associated cognitive deficits, suggesting its role in mitigating inflammation-induced depression (Worthen et al., 2020). IL-10's anti-inflammatory effects make it a candidate for counteracting the inflammatory milieu contributing to depression; therefore, when IL-10 levels are reduced, they fail to suppress pro-inflammatory cytokines, exacerbating depressive symptoms (Yin et al., 2024).

QoL measures, such as physical functioning, vitality, and general health correlated positively with IL-10. Although we could not find studies explicitly discussing the relationship between IL-10 level and quality of life parameters, this positive correlation can be attributed to its systemic anti-inflammatory effects. Chronic inflammation is a major contributor to fatigue, reduced physical capacity, and general malaise, which negatively impact QoL (Russell et al., 2011). IL-10 counteracts systemic inflammation, potentially alleviating these symptoms and promoting a sense of vitality.

5.4. CHI3L1 as a chronic neuroinflammation marker

CHI3L1 correlated positively with the total number of relapses ($P = 0.021$) and EDSS ($P = 0.001$) and had a negative correlation with Physical function, energy/fatigue, social, and general health domains of QoL ($P = 0.001$, 0.009, 0.03, and 0.013, respectively).

In contrast to IL-10, CHI3L1 exhibited positive correlations with the total number of relapses and EDSS, consistent with its role as a marker of chronic glial activation and ongoing neuroinflammation. Higher level of CHI3L1 had a negative impact on vitality, social, and general health domains of QoL, This suggests that CHI3L1 may serve as a marker for cumulative neurodegeneration over time but contributes less to

functional or QoL outcomes that aligning with its implication in systemic inflammation (Floro et al., 2022; Jatczak-Pawlik et al., 2024; Talaat et al., 2023).

IL-10 represents the body's counter-regulatory response to suppress inflammation and promote repair, which may differ across individuals and disease phases. The negative correlation between IL-10 and CHI3L1 may represent an intrinsic regulatory mechanism in which an increase in anti-inflammatory IL-10 reduces the inflammatory signals driving CHI3L1 production.

5.5. *Clinical implications and future directions for biomarker research in MS*

The findings of this study underscore the clinical relevance of IL-10 as a candidate biomarker for stratifying MS patients based on disease burden, and quality of life, particularly in the early phases of disease before the initiation of treatment. In clinical practice, IL-10 could potentially be used to identify patients with a lower likelihood of relapse or aiding in treatment selection and monitoring. Its incorporation alongside neuroimaging data, and neurofilament light chain, could enhance diagnostic precision and disease stratification. Overall, this study paves the way for a precision medicine approach in MS where IL-10, integrated with clinical, and imaging markers, contributes to earlier diagnosis, improved monitoring, and individualized treatment strategies.

5.5.1. *Strengths of the study*

The study includes a well-characterized cohort of DMT-naïve MS patients, eliminating the potential confounding effects of immunotherapy on biomarker levels. The evaluation of both IL-10 (anti-inflammatory) and CHI3L1 (pro-inflammatory) enables a comparative analysis of protective and pathogenic mechanisms. A comprehensive assessment was performed, including demographic, clinical, cognitive, and quality-of-life parameters, providing a multidimensional profile of disease burden. Biomarker measurements were performed using validated, high-sensitivity sandwich ELISA kits, ensuring methodological reliability.

5.5.2. *Limitations*

The cross-sectional design limits inference on causal or temporal relationships between biomarkers and clinical progression. The overall sample size, especially for subgroup analysis, restricts generalizability. The study focused on serum rather than CSF biomarkers, which may not fully represent CNS-specific processes. External validation in larger, longitudinal, and treatment-diverse cohorts is necessary to confirm findings and assess biomarker dynamics over time.

6. Conclusion

This study highlights IL-10 as a promising serum biomarker with potential neuroprotective and anti-inflammatory roles in multiple sclerosis. Higher IL-10 levels were associated with lower relapse rates, reduced depression, and improved quality of life in DMT-naïve RRMS patients. In contrast, CHI3L1 was more reflective of chronic disease burden and cumulative neuroinflammation and just predictive of functional outcomes. These findings support the utility of IL-10 in the early identification of favorable disease profiles and personalized management strategies. Further longitudinal and mechanistic studies are warranted to validate IL-10′s prognostic value and explore therapeutic modulation of the IL-10 axis in MS.

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CRediT authorship contribution statement

Eman M Khedr: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hussein Bahey El-Deen:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Mohamed A El-Mokhtar:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Doaa M. Mahmoud:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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