

Original article

## Assessing the Relationship of CRP and ESR Inflammatory Biomarkers with Acute Multiple Sclerosis Attack and Clinical Syndrome Type in Patients Attending Selected Tehran Hospitals

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**Abstract: Background** — Multiple sclerosis (MS) is a chronic progressive neurological disease that results in the expansion of pathological pathways of neuronal destruction, such as neuroaxonal injury, apoptosis, and gliosis. Due to the complexity of the mechanisms involved in the pathophysiology of multiple sclerosis, finding reliable biomarkers is a challenging task. However, it is of utmost importance to identify effective biomarkers with high sensitivity that can determine the level of disease activity and progression.

**Objective** — The goal of this study was to specify the relationship between inflammatory biomarkers, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), with acute attacks of MS and the type of clinical syndrome in patients attending Baqiyatallah Al-Azam and Shahid Mostafa Khomeini Hospitals from 2017 to 2021.

**Methods** — This retrospective study was conducted in the above-mentioned medical centers. Initially, the medical records of all patients attending these medical centers for diagnosis and treatment of MS were reviewed. Then, the medical records of patients with acute attacks of MS diagnosed by a neurologist who met the inclusion criteria and were available at the time of the study were selected. Data were collected using a form designed by the investigator; it included personal characteristics, laboratory results of ESR, CRP, prognosis assessment (score), and clinical symptoms of the patients. The current prognosis score of the patients was determined based on the most recent medical examination. Data analysis was performed using logistic regression models and SPSS-16 statistical software.

**Results** — Our data showed that ESR increased statistically significantly in individuals over 35 years of age vs. those under 35 years of age ( $P=0.024$ ). In females, the changes in Expanded Disability Status Scale (EDSS) score were more significant than in males ( $P=0.018$ ). ESR increased significantly in clinical syndrome of hemiparesis ( $P=0.018$ ) and spinal syndrome ( $P=0.007$ ). In women with clinical evidence of the optic neuritis syndrome, there was a significant increase in CRP ( $P=0.020$ ). In women with clinical evidence of the hemiparesis syndrome, the changes in EDSS score were statistically significant ( $P=0.043$ ).

**Conclusion** — The likelihood of increasing the level of the inflammatory biomarker ESR during acute attacks of MS is higher compared with CRP. Moreover, the increase in ESR and CRP was found to be useful for the differentiation and diagnosis of various clinical syndromes.

**Keywords:** multiple sclerosis, C-reactive protein level, erythrocyte sedimentation rate, prognosis.

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### Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system that mainly affects younger people, with the onset in patients between the ages of 20 and 40 years. Recently, the incidence and prevalence of MS have increased worldwide [1]. Central nervous system lesions cause various symptoms in patients with MS that affect motor, sensory, visual or autonomic functions. It can manifest itself in different forms, such as primary progressive (PPMS), secondary progressive (SPMS), progressive-relapsing (PRMS) and relapsing-remitting (RRMS). The latter is the most common form of MS [2]. MS shows significant heterogeneity in terms of radiological and histopathological changes, clinical presentation and progression, and response to treatment.

Therefore, it is of paramount importance to define specific characteristics of the disease that facilitate diagnosis and prognosis and allow the assessment of treatment response and the risk of side effects [3]. Characteristics such as relapse rate and disability progression play the most important roles. However, although it is possible to quantify and standardize these characteristics in larger patient groups, this is not yet possible in individual patients [4]. Although the importance of molecular biomarkers has been increasingly recognized in recent years, their validation is a lengthy process and so far, only a few biomarkers have been widely used in clinical practice. Nevertheless, the number of potential biomarkers at various stages of testing is promising. This study describes the characteristics that an ideal MS biomarker should have and the challenges in developing new biomarkers [5]. In addition, clinically relevant and promising

biomarkers in blood and cerebrospinal fluid (CSF) are presented that are useful for the diagnosis and prognosis of MS, as well as for assessing response to therapy and side effects [6]. Despite an active search for biomarkers, no laboratory test with 100% specificity for MS has been developed so far. However, findings such as elevated ESR and lymphopenia suggest the need to investigate for systemic disease [7]. Given the importance of the disease and its economic burden, we aimed to evaluate serum levels of inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), during acute attacks in patients with MS and compare them with clinical syndromes and prognoses in these patients in a retrospective manner.

## Material and Methods

### Sample size

The sample size was calculated based on the Cochran formula, taking into account 200 referrals to Baqiyatallah Hospital and Mostafa Khomeini Hospital in Tehran from 2017 to 2021. Due to the lack of information on the prevalence of the disease, a maximum prevalence of 50% and a margin of error of 5% (0.05) were used, which resulted in a sample size of 131 individuals.

$$n = \frac{nZ^2pq}{nd^2 + Z^2pq} = n = \frac{200 \times 1.96^2 \times 0.5 \times 0.5}{200 \times 0.05^2 + 1.96^2 \times 0.5 \times 0.5} = 131$$

**Table 1.** Demographic and laboratory data of patients with multiple sclerosis referred to Baqiyatallah and Shahid Mostafa Khomeini hospitals

| Variable                                                          | Category       | Number (%) |
|-------------------------------------------------------------------|----------------|------------|
| Gender                                                            | Male           | 39 (29.8)  |
|                                                                   | Female         | 92 (70.2)  |
| Age, years                                                        | 15-35          | 67 (51.1)  |
|                                                                   | 35-60          | 64 (48.09) |
| Marriage                                                          | Single         | 31(23.7)   |
|                                                                   | Married        | 100 (76.3) |
| Clinical syndrome                                                 | Cerebellar     | 28 (21.4)  |
|                                                                   | Hemiparesis    | 33(25.2)   |
|                                                                   | Optic neuritis | 39 (29.7)  |
|                                                                   | Spinal         | 31(23.7)   |
| ESR, mm/h                                                         | Normal         | 105 (80.2) |
|                                                                   | Abnormal       | 26 (19.8)  |
| CRP, mg/L                                                         | Normal         | 108 (82.4) |
|                                                                   | Abnormal       | 23 (17.6)  |
| Type of change in EDSS score between current time and attack time | No change      | 47 (35.9)  |
|                                                                   | Increase       | 84 (64.1)  |

**Table 2.** Association of ESR and CRP biomarkers and EDSS score changes with demographic variables in patients with multiple sclerosis referred to Baqiyatallah and Shahid Mostafa Khomeini hospitals

| Syndrome        | Variable   | Category | Reference | IF (β) | SD   | P-value* | Odds ratio |
|-----------------|------------|----------|-----------|--------|------|----------|------------|
| Female          | ESR        | Abnormal | Normal    | -0.05  | 0.47 | 0.901    | 0.94       |
| 35-60 years old | ESR        | Abnormal | Normal    | 1.06   | 0.46 | 0.024    | 2.8        |
| Married         | ESR        | Abnormal | Normal    | -0.04  | 0.51 | 0.937    | 0.96       |
| Female          | CRP        | Abnormal | Normal    | 0.50   | 0.54 | 0.357    | 1.6        |
| 35-60 years old | CRP        | Abnormal | Normal    | 0.16   | 0.46 | 0.726    | 1.1        |
| Married         | CRP        | Abnormal | Normal    | -0.15  | 0.52 | 0.764    | 0.85       |
| Female          | EDSS score | Increase | Constant  | 0.93   | 0.39 | 0.018    | 2.5        |
| 35-60 years old | EDSS score | Increase | Constant  | 0.12   | 0.36 | 0.726    | 1.1        |
| Married         | EDSS score | Increase | Constant  | 0.16   | 0.42 | 0.707    | 1.1        |

\*binary regression; reference: gender=male, age=15-35 years, marital status=single; IF, impact factor; SD, standard deviation.

### Data collection instruments

We used clinical data recorded in patient records at the time of attacks and discharge. The Expanded Disability Status Scale (EDSS) is a method used to measure the degree of disability in individuals with MS. The scale was developed in 1955 by John Francis Kurtzke. Although the EDSS is the most widely used measure of disability progression in MS, it has been criticized for its limitations. For example, EDSS score can vary due to complex scoring rules and the subjective nature of neurological examination. Some argue that changes between scale steps (e.g., 1 to 2 and 4 to 5) are dissimilar, and that from a score of 4 pts onward, the scale overly focuses on walking ability, thereby underestimating the importance of upper body function in self-care and independence. It was also highlighted that some functional domains such as cognitive abilities, mood, energy level and quality of life were not assessed adequately. Wallenstein et al. reported a test-retest reliability of 0.6 to 0.7 for this instrument. Its validity was also found to be high compared with the VAS and SF36 instruments.

### Study population

The study sample included all patients aged 15 to 70 years with a diagnosis of MS, hospitalized by a neurologist due to acute attacks of MS in the past 5 years and whose medical records were available.

### Inclusion criteria

The inclusion criteria for the study were as follows: no concomitant acute infection during the acute attack, no autoimmune diseases or malignancies during the acute attack, no recent antibiotic use during the acute attack, no pulse corticosteroid therapy during the acute attack before ESR and CRP measurement, no pregnancy in women during the acute attack, and no gaps in the patients' medical records.

### Sampling procedure

The sample was selected using convenience sampling.

### Statistical data processing

Descriptive analysis was performed to summarize the patients' demographic data and the frequency of clinical manifestations. Laboratory parameters were classified as *normal* or *abnormal*. Cutoff values for ESR and CRP tests were specified based on established scientific standards and clinical guidelines as follows:

– ESR: normal values were defined as ≤20 mm/h for women and ≤15 mm/h for men;

– CRP: values <10 mg/L were considered normal, whereas values above this limit were classified as abnormal. The dependent variable was the change in patients' EDSS scores between the attack and follow-up. These changes were grouped into two categories: *increase* (higher score at follow-up) or *no change*.

A multivariate binary logistic regression model was employed to assess the association of demographic variables (e.g., gender, age, and marital status) and laboratory biomarkers (CRP and ESR) with EDSS scores and their changes. In this model, the dependent variable is binary (increase or no change in EDSS score), and the independent variables include gender, age group, CRP level (normal or abnormal), ESR (normal or abnormal), and other

demographic factors such as marital status. Odds ratios (ORs) were presented along with  $\beta$  coefficients, standard deviations of the coefficients, and significance levels (P-values) for each variable. All statistical analyses were performed using SPSS version 21 with a significance level of less than 0.05.

**Table 3.** Association of ESR and CRP biomarkers with clinical syndrome and associated EDSS score changes in multiple sclerosis patients referred to Baqiyatullah and Shahid Mostafa Khomeini hospitals

| Syndrome       | Variable | Category | Reference | IF ( $\beta$ ) | SD    | P-value | Odds ratio |
|----------------|----------|----------|-----------|----------------|-------|---------|------------|
| Cerebellar     | ESR      | Abnormal | Normal    | -0.77          | 0.66  | 0.240   | 0.46       |
| Optic neuritis | ESR      | Abnormal | Normal    | -0.57          | 0.54  | 0.290   | 0.56       |
| Hemiparesis    | ESR      | Abnormal | Normal    | 1.27           | 0.55  | 0.017   | 1.05       |
| Spinal         | ESR      | Abnormal | Normal    | 1.31           | 0.48  | 0.007   | 1.70       |
| Cerebellar     | CRP      | Abnormal | Normal    | -0.28          | 0.67  | 0.678   | 0.75       |
| Optic neuritis | CRP      | Abnormal | Normal    | 0.88           | 0.53  | 0.099   | 2.41       |
| Hemiparesis    | CRP      | Abnormal | Normal    | -1.01          | 0.78  | 0.195   | 0.36       |
| Spinal         | CRP      | Abnormal | Normal    | -0.02          | 0.61  | 0.964   | 0.97       |
| Cerebellar     | EDSS     | Increase | Normal    | -0.45          | 0.46  | 0.327   | 0.63       |
| Optic neuritis | EDSS     | Increase | Constant  | 0.38           | 0.44  | 0.388   | 1.47       |
| Hemiparesis    | EDSS     | Increase | Constant  | 0.03           | 0.45  | 0.937   | 1.03       |
| Spinal         | EDSS     | Increase | Constant  | 0.02           | -0.46 | 0.951   | 0.97       |

F, impact factor; SD, standard deviation.

**Table 4.** Association of ESR and CRP biomarkers with clinical syndromes and corresponding changes in EDSS score depending on gender

| Syndrome       | Variable | Category | Reference | IF ( $\beta$ ) | SD    | P-value | Odds ratio |
|----------------|----------|----------|-----------|----------------|-------|---------|------------|
| Cerebellar     | ESR      | Abnormal | Normal    | -0.93          | 1.28  | 0.469   | 0.39       |
| Optic neuritis | ESR      | Abnormal | Normal    | -0.33          | 0.98  | 0.736   | 0.71       |
| Hemiparesis    | ESR      | Abnormal | Normal    | 0.35           | 1.18  | 0.764   | 1.42       |
| Spinal         | ESR      | Abnormal | Normal    | -0.57          | 0.91  | 0.530   | 0.56       |
| Cerebellar     | CRP      | Abnormal | Normal    | 0.31           | 1.004 | 0.751   | 1.37       |
| Optic neuritis | CRP      | Abnormal | Normal    | 1.84           | 1.11  | 0.020   | 6.5        |
| Hemiparesis    | CRP      | Abnormal | Normal    | -1.42          | 1.48  | 0.337   | 0.24       |
| Spinal         | CRP      | Abnormal | Normal    | 0.22           | 1.20  | 0.853   | 1.2        |
| Cerebellar     | EDSS     | Increase | Normal    | 1.48           | 0.81  | 0.049   | 4.4        |
| Optic neuritis | EDSS     | Increase | Constant  | 0.52           | 0.72  | 0.464   | 1.6        |
| Hemiparesis    | EDSS     | Increase | Constant  | 1.91           | 0.94  | 0.043   | 6.7        |
| Spinal         | EDSS     | Increase | Constant  | -0.11          | 0.96  | 0.902   | 0.88       |

Reference: gender=male; IF, impact factor; SD, standard deviation.

**Table 5.** Association of ESR and CRP biomarkers with clinical syndromes and corresponding changes in EDSS score depending on age

| Syndrome       | Variable | Category | Reference | IF ( $\beta$ ) | SD   | P-value | Odds ratio |
|----------------|----------|----------|-----------|----------------|------|---------|------------|
| Cerebellar     | ESR      | Abnormal | Normal    | NM             | NM   | NM      | NM         |
| Optic neuritis | ESR      | Abnormal | Normal    | 1.28           | 0.98 | 0.195   | 3.6        |
| Hemiparesis    | ESR      | Abnormal | Normal    | 0.37           | 0.90 | 0.976   | 1.4        |
| Spinal         | ESR      | Abnormal | Normal    | 0.56           | 0.81 | 0.494   | 1.7        |
| Cerebellar     | CRP      | Abnormal | Normal    | 1.2            | 1.1  | 0.276   | 3.6        |
| Optic neuritis | CRP      | Abnormal | Normal    | -1.8           | 1.1  | 0.099   | 0.15       |
| Hemiparesis    | CRP      | Abnormal | Normal    | 0.32           | 1.4  | 0.824   | 1.3        |
| Spinal         | CRP      | Abnormal | Normal    | NM             | NM   | NM      | NM         |
| Cerebellar     | EDSS     | Increase | Normal    | -1.3           | 0.83 | 0.106   | 0.25       |
| Optic neuritis | EDSS     | Increase | Constant  | 1.23           | 0.86 | 0.155   | 3.4        |
| Hemiparesis    | EDSS     | Increase | Constant  | 0.59           | 0.75 | 0.427   | 1.8        |
| Spinal         | EDSS     | Increase | Constant  | 0.28           | 0.79 | 0.717   | 1.3        |

Reference: age=15-35 years; NM = not measurable due to lack of frequency.

## Results

The study included 131 patients with MS who were referred to Baqiyatallah and Shahid Mostafa Khomeini Hospitals in Tehran, Iran. The patients' ages ranged from 15 to 60 years, with a mean age of  $34.78 \pm 10.05$  years. Notably, 51.1% of the patients were in the 15-35 years age group, implying that most of the patients who were diagnosed at the time of referral were young or middle-aged. Among the participants, there were 92 (70.2%) females and 39 (29.8%) males, corresponding to a female to male ratio of approximately 2.4:1. Also, 76.3% of the patients were married ([Table 1](#)).

The most common clinical syndrome was optic neuritis (29.7%), while the least common was cerebellar syndrome (21.4%). The ESR biomarker ranged from 0 to 83 mm/h, with a median of 11 mm/h (5-18 mm/h). Elevated ESR levels above normal were found in 26 patients (19.8%). Similarly, the CRP biomarker ranged from 0 to 49.6 mg/L, with a median of 4.2 (2.8-7) mg/L. Elevated CRP levels were found in 23 patients (17.6%). EDSS scores during attacks ranged from 0 to 4 pts, with a median of 1 (0-2) pt. During follow-up, scores ranged from 0 to 7 pts, with a median of 1 (1-2) pt. Elevated EDSS scores were observed in 84 patients (64.1%).

The estimated effect size ( $\beta=1.06$ ) for abnormal value of ESR biomarker in individuals aged 35-60 years vs. those aged 15-35 years demonstrates a direct association between increasing age and the odds of abnormal ESR. This indicates that, on average, the odds of observing an abnormal ESR increase with age ([Table 2](#)). This direct effect is statistically significant ( $P=0.024$ ). Moreover, individuals aged 35-60 years are 2.8 times more likely to exhibit abnormal ESR value than those aged 15-35 years.

Similarly, the estimated effect size ( $\beta=0.93$ ) for current EDSS score changes compared with its value at the time of the attack shows a significant direct association between EDSS score change in females vs. males. This suggests that females are more likely to exhibit increased current score vs. pre-attack EDSS score. This association is also statistically significant ( $P=0.018$ ). In addition, women are 2.5 times more likely to have an increase in EDSS score at present than men. No statistically significant associations were found with other examined demographic factors ( $P>0.05$ ).

The estimated effect size ( $\beta=1.27$ ) for abnormal ESR biomarkers in hemiparesis syndrome suggests a significant direct association between the condition and the odds of abnormal ESR. This indicates that individuals with hemiparesis syndrome are more likely to have abnormal ESR levels, and the effect is statistically significant ( $P=0.017$ ). Specifically, the odds of abnormal ESR in hemiparesis syndrome are 1.05 times higher than in individuals without the syndrome ([Table 3](#)).

Similarly, the estimated effect size ( $\beta=1.31$ ) for abnormal ESR biomarker in spinal syndrome shows a significant direct association between the syndrome and the odds of abnormal ESR. This indicates that individuals with spinal syndrome are more likely to have abnormal ESR levels, and the effect is statistically significant ( $P=0.007$ ). The odds of abnormal ESR in spinal syndrome are 1.7 times higher than in individuals without the syndrome. In contrast, no significant associations were revealed between other biomarkers or changes in EDSS scores and clinical syndromes in patients with MS ( $P>0.05$ ).

A regression model analyzing gender differences in clinical syndromes revealed notable results. Compared with men, women had a 6.5-fold higher increase in the CRP biomarker in optic

neuritis syndrome, which was statistically significant ( $P=0.020$ ). Similarly, in cerebellar syndrome, women had a 4.4-fold higher increase in EDSS score compared with men, which was also statistically significant ( $P=0.049$ ). In hemiparesis syndrome, women had a 6.7-fold higher increase in EDSS score than men, which also reached statistical significance ( $P=0.043$ ). However, other syndromes showed no significant effect on biomarkers or EDSS score change ( $P>0.05$ ) (Table 4).

The age-based regression model of clinical syndromes showed that they did not have a significant impact on biomarkers and changes in EDSS score ( $P>0.05$ ) (Table 5).

## Discussion

The present study showed that the ESR inflammatory marker has the highest increase in spinal and hemiparesis syndromes, and this increase was statistically significant. No significant difference was observed between the two syndromes (spinal and hemiparesis). Clinical syndromes did not have a significant effect on the increase in CRP biomarker and the change in EDSS score. These findings are consistent with the study of Nazari et al. regarding cerebellar syndrome and optic neuritis. However, they are not consistent with the data regarding spinal and hemiparesis syndromes. The reason for this difference may be related to the selection of patient types: the above-mentioned study examined patients in the acute and relapse stages of the disease, while the present study assessed only the acute stage. In addition, the previous study focused on new patients compared to existing patients, while the current study did not make such a comparison [8].

Regarding the lack of influence of optic neuritis syndrome on the biomarkers ESR and CRP, the results are consistent with the study by Bisgaard, but not with respect to the EDSS score. The reason for the difference may be due to the classification of optic neuritis; in the previous study, it was classified into primary progressive, secondary progressive, and relapsing syndromes, which was different from the classification in the current study [9]. The lack of influence of optic neuritis syndrome on the ESR and CRP biomarkers is also consistent with the study by Cheng, but not with respect to the EDSS score. The reason for the difference may be due to the classification of patients; in the previous study, patients were classified into three groups: with extensive brain lesions, without extensive brain lesions, and without brain lesions, while in the current study, brain lesions were not taken into account [10].

Based on our results, we suggest that in spinal and hemiparesis syndromes, the probability of increasing the ESR biomarker is higher than CRP, but further studies are needed. The current study also showed that in optic neuritis syndrome, the increase in the CRP biomarker was greater in women than in men, while in hemiparesis syndrome, the changes in EDSS score were greater in women than in men. Other clinical syndromes did not have a significant effect on the changes in biomarkers and EDSS score based on gender and age.

Regarding the effect of gender on the increase in ESR based on clinical syndrome, the results are consistent with the study by Milstein et al., but not for the CRP biomarker. The reason for the difference may be related to the patient selection; in the previous study, gender was considered based on clinical syndrome in different ethnic groups, while in the current study, clinical

syndrome was considered separately based on gender and age [11].

## Conclusion

Our results suggest that ESR is more closely associated with acute MS attacks and specific clinical syndromes (hemiparesis, spinal) than CRP, with notable gender differences in biomarker values and disability outcomes. Further studies are needed to fully understand the relationship between these biomarkers and the complex mechanisms of MS development.

## Limitations

Although our results provide a foundation for the investigation of ESR and CRP in MS, the study had several limitations, including the need for a prospective design, larger sample sizes, and integration with imaging and CFS markers, which should be considered in future studies.

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## Conflict of interest

The authors declare no conflicts of interest.

## Ethical approval

This study received approval from the Research Ethics Committee of Shahed University (the reference number IR.SHAHED.REC.1400.213). Formal consent is not required for this type of study.

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