Received: 1 December 2023 | Accepted: 15 February 2024

DOI: 10.1111/ijlh.14259

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

Neutrophil to lymphocyte ratio and systemic immune-inflammatory index as markers of response to autologous hematopoietic stem cell transplantation in persons with multiple sclerosis

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Abstract

Introduction: Biomarkers that help to evaluate the immune system and could be useful in multiple sclerosis (MS) are the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII). The objective of this work is to evaluate the significance of the SII index, PLR, and NLR before and after transplantation in individuals with MS who underwent autologous hematopoietic stem cell transplant (aHSCT) at a single institution.

Methods: Patients with MS who received an aHSCT between 2017 and 2022 were included in the study. NLR, PLR, and SII index were calculated prior to the transplant and 100 days after, and evaluation of the expanded disability status scale (EDSS) was done before the transplant and 12 months after. The cohort was divided into two groups: aHSCT responders (R) and nonresponders (NR).

Results: Fifty-eight individuals were examined: 37 patients in the responders group R group and 21 in NR group. There was no statistically significant difference in the SII, NLR, and PLR prior to the transplant, however at 100 days post-HSCT, NLR in the R group was 1.8 versus 3.1 in the NR group ($p = 0.003$), PLR was 194 versus

Abbreviations: aHSCT, Autologous hematopoietic stem cell transplant; CRP, C-reactive protein; EDSS, Expanded disability status scale; Lymph, Absolute lymphocyte count; MS, Multiple sclerosis; Neut, Neutrophils; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; Plt, Platelets; PPMS, Primary progressive multiple sclerosis; RRMS, Relapsing remitting multiple sclerosis; SII, Systemic immune-inflammatory index; SPMS, Secondary progressive multiple sclerosis; WBC, White blood cell.

295, respectively ($p = 0.024$), meanwhile SII index was 489.5 versus 729.3 ($p < 0.001$).

Conclusion: High NLR and SII index values after the aHSCT were associated with a worsening in the EDSS score. However, since this is the first ever study that compared NLR and SII index with the aHSCT response in persons with MS, further studies must be performed to corroborate this information.

KEYWORDS

autologous hematopoietic stem cell transplant, biomarker, disease progression, multiple sclerosis, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, systemic immune-inflammatory index

1 | INTRODUCTION

The clinical course of multiple sclerosis (MS) is known to be complex, characterized by a sequence of events involving neuroinflammation, followed by demyelination and axonal degeneration. This disease has significant economic and social implications, affecting a global population of over 2 million individuals.[1] Consequently, the investigation of MS has garnered great importance, particularly in the search for novel biomarkers and therapeutic options. Unlike other autoimmune disorders, where multiple biomarkers have proven useful in diagnosis and monitoring, the identification of reliable peripheral biomarkers in MS has been a long-standing challenge that has thus far yielded limited success. This can be attributed to the poor correlation between neuroinflammation, a key feature of the disease, and the currently available blood markers of inflammation, such as C-reactive protein (CRP) or uric acid.[2,3] The relationship between immune cells and the processes of neuroinflammation and demyelination remains poorly understood.

It has been acknowledged that neutrophils and platelets are useful biomarkers in different conditions such as sepsis or trauma.[4] In central nervous system (CNS) autoimmunity there is growing evidence that these peripheral biomarkers have an important participation.[5,6] In contrast to healthy controls, MS patients have a higher neutrophil to lymphocyte ratio (NLR) that apparently increases with the onset of relapses.[5] NLR is a biomarker used to determine the response of the innate and adaptative immune system, mediated by neutrophils and lymphocytes, respectively.[7] NLR easily assesses patient's inflammatory response to acute and chronic diseases,[8] it has been extensively used as a prognostic factor in different types of cancers and hematological malignancies, activity marker in autoimmune diseases and to predict preoperative outcomes,[9–14] yet the research of NLR in MS is heterogeneous.[3,15–18]

Systemic immune-inflammatory index (SII) is a novel index, first employed by the Liver Cancer Institute in Shanghai in 2014.[19] It uses the NLR and multiplies it by the platelet count, giving as a result a reliable inflammatory index. SII has been used to evaluate a broad spectrum of diseases where inflammation and immunity are involved, such as diverse solid and hematological malignancies and cardiovascular diseases.[19–21]

Most of the drugs available for the treatment of MS have significant effects in the immune system. Autologous hematopoietic stem cell transplantation (aHSCT) has been a therapeutic option for patients with MS since the 1990's,[22] especially in patients with no response to disease modifying therapy. The aHSCT regimen consists of high-dose chemotherapy/immunotherapy followed by rescue of the bone marrow function with autologous hematopoietic stem cells.[23] It is believed that the immunological system suffers a "reset" after the delivery of chemotherapy/immunotherapy to baseline functions, thus modifying the progression of the disease.[23] After a hematological recovery, the SII index, the ratio of neutrophils to lymphocytes and platelets to lymphocytes could be markers of aHSCT response in patients with MS.

The objective of this article is to assess the significance of the SII index, PLR, and NLR before and after transplantation in individuals with MS who underwent aHSCT at a single institution, considering the increasing body of evidence indicating the essential role of neutrophils and platelets in CNS autoimmunity and in the pathogenesis of MS.

2 | METHODS

2.1 | Patients

Patients with MS who received an aHSCT between 2017 and 2022 and who had a follow-up at the 12-month mark were included in the study. Blood work was done prior transplant and on day 100 afterwards. Evaluation of the expanded disability status scale (EDSS) by a certified neurologist was done before the transplant and 12 months after. EDSS is the scale that is most frequently utilized in patients with MS. The evaluation of EDSS is executed through the utilization of a nonlinear assessment, whereby MS is assessed on a scale ranging from 0 to 10. It is notable that a normal neurological examination results in an EDSS assessment of 0, whereas an evaluation of 10 signifies death related to MS.[24] Diagnosis of MS was done according to the McDonald criteria.[25] NLR, PLR, and SII index were calculated prior to the transplant and 100 days after. The response to the transplant was evaluated by calculating the difference in the EDSS prior to the transplant and the EDSS 12 months after. The cohort was divided into two groups: HSCT responders (R) and nonresponders (NR);

responders included both stabilization and improvement in the EDSS score. None of the patients received immunosuppressive therapy for at least 3 months prior to the aHSCT, and after being informed about the procedure and possible complications, signed a consent form.

Patients were classified as relapsing remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), and secondary progressive multiple sclerosis (SPMS) according to their clinical context. RRMS is characterized by episodes of acute exacerbations, during which patients experience either complete or partial recovery, with periods of clinical stability in between. On the other hand, PPMS classification encompasses patients who exhibit a continuous decline in neurological function from the very onset of the disease. As for SPMS, it is defined by a gradual progression of symptoms following an initial course of relapses, affecting approximately 40% of patients within 20 years of the initial event.[26]

2.2 | Equipment and parameters

The equipment used for the data processing of the pre-transplant blood work was the Coulter LH780 Hematology Analyzer (Beckman Coulter de México, Mexico) at Laboratorios Ruiz in Puebla, Mexico. Internal quality control is performed twice daily with first opinion reagents and participation in the Interlaboratory Quality Assurance Program of Beckman Coulter. External quality evaluation is performed with the help of the FH-13 proficiency test program offered by CAP which covers all relevant parameters included in the current study in five challenges three times a year. The test is accredited by ema under the ISO 15189 standard. Complete blood counts (CBC) with differentials were measured and indices were obtained.

Platelets were analyzed with Sweep Flow technology.

CRP was assessed through the utilization of an enzymatic immunoassay, employing nephelometry as the method of measurement on the BN ProSpec System (Siemens Healthineers, Mexico City) at Laboratorios Ruiz in Puebla, Mexico. Quality is controlled internally twice a day by using first opinion reagents covering three concentration levels. For the external quality evaluation, the test participates in the BioRad EQAS program three times annually. The test is accredited by ema under the ISO 15189 standard.

NLR was calculated as: absolute neutrophil count (10^3/μL)/absolute lymphocyte count (10^3/μL). PLR (platelet to lymphocyte ratio) was calculated as: absolute platelet count (10^3/μL)/absolute lymphocyte count (10^3/μL) SII was calculated as: absolute platelet count (10^3/μL) × (absolute neutrophil count [10^3/μL]/absolute lymphocyte count [10^3/μL]).

Post-transplant blood work was evaluated in each patient's country of residence.

2.3 | Peripheral blood stem cell mobilization and apheresis

The aHSCT was done employing the Mexican method[27]; the protocol has been registered at ClinicalTrials.gov identifier NCT02674217. All patients were subjected to peripheral blood stem cell (PBSC) mobilization administering intravenous cyclophosphamide (Cy) 50 mg/kg, followed by MESNA 1000 mg/m^2 on days −11 and − 10 and subcutaneous filgrastim (C-CSF) 10 μg/kg/ bid was given from day −9 to −1. Apheresis was performed on day −2, obtaining >1 × 10^6 viable CD34$^+$ cells/Kg of the patient.

2.4 | Autografting

On days −2 and −1, after the collection of CD34$^+$ cells, IV Cy 50 mg/kg and MESNA 1000 mg/m^2 were administered on each day. All patients received ondansetron 4 mg after every chemotherapy pantoprazole 40 and dexamethasone 4 mg every 24 h throughout the whole process. Reinfusion was done on day 0. Oral fluconazole (200 mg every 24 h), oral cotrimoxazole (800/160 mg every 24 h), and oral acyclovir (400 mg bid) were administered until hematological recovery (granulocytes >0.5 × 10^9/L). Clinical evaluation along with laboratory tests were performed every 48 h. Rituximab (1000 mg) was administered in a 3 h period, after leukocytes increased above 4.0 × 10^9/L. All patients included in our study were taking cotrimoxazole 800/160 mg bid, three times a week and acyclovir 800 mg every 24 h for 6 months as prophylactic therapy for infections prevention after the aHSCT.

2.5 | Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the normality of the distribution of the data to be analyzed. The data in our study do not conform to a normal distribution, so the Mann–Whitney *U* test was used to comparison of both groups (R vs NR) and Chi-square test was employed for the comparison of qualitative variables. Results with p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS 25 software (IBM Corp. Published 2017 IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) and GraphPad Prism 9 (GraphPad Prism version 9 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com).

3 | RESULTS

3.1 | Demographic findings and status before aHSCT

Fifty-eight participants were enrolled in this investigation, with 47 females and 11 males. The median ages in the two cohorts were 49 years for the R cohort and 45 years for the NR cohort. The mean duration of disease progression was 7 and 6 years, correspondingly ($p = 0.820$). Within the R cohort, five patients were diagnosed with PPMS, 26 with RRMS, and 6 with SPMS. In the NR

TABLE 1 Clinical features of the 58 patients.

	Response	No response	*p*
Age	49 (42–53)	45 (40–51)	0.270 [a]
Female	30	17	0.99 [b]
Male	7	4	
Evolution time (Years)	7 (2–13)	6 (3–14)	0.820 [a]
EDSS pre-HSCT	5 (3–6)	3.5 (2–5.5)	0.069 [a]
EDSS post-HSCT	4 (2–5.5)	5 (4–6.5)	0.007 [a]
PPMS	7 (2–13)	6 (3–14)	0.232 [b]
RRMS	5 (3–6)	3.5 (2–5.5)	
SPMS	4 (2–5.5)	5 (4–6.5)	
WBC pre-HSCT (10^3/μL)	5.8 (4.8–6.8)	5.9 (4.7–8.5)	0.655 [a]
WBC post-HSCT (10^3/μL)	4.2 (3.3–5.2)	4.1 (2.8–5.4)	0.775 [a]
NEUT pre-HSCT (10^3/μL)	3.2 (2.7–3.9)	3.6 (2.7–5)	0.344 [a]
NEUT post-HSCT (10^3/μL)	2.3 (1.9–2.9)	2.5 (1.8–3.9)	0.264 [a]
LYMPH pre-HSCT (10^3/μL)	1.8 (1.1–2.3)	1.7 (1–2.5)	0.850 [a]
LYMPH post-HSCT (10^3/μL)	1.2 (0.9–1.7)	0.7 (0.6–1.3)	0.029 [a]
PLT pre-HSCT (10^3/μL)	247 (218–283)	257 (230–293)	0.374 [a]
PLT post-HSCT (10^3/μL)	238 (194–301)	255 (207–318)	0.361 [a]
NLR pre-HSCT	2 (1.3–2.8)	2.2 (1.7–3.9)	0.361 [a]
NLR post-HSCT	1.8 (1.4–2.3)	3.1 (2.2–3.7)	0.003 [a]
PLR pre-HSCT	139.6 (103.4–196.7)	147.7 (123.4–235.0)	0.512 [a]
PLR post-HSCT	194.7 (157.6–289.3)	295.8 (194.8–376.8)	0.024 [a]
SII pre-HSCT	494.1 (345.9–630.7)	630.7 (397.5–904.8)	0.219 [a]
SII post-HSCT	489.5 (306–631.7)	729.3 (549.8–1152.6)	<0.001 [a]
CRP pre-HSCT (mg/L)	0.5 (0.3–1.3)	0.6 (0.4–1.4)	0.700 [a]

Abbreviations: CRP, C-reactive protein; EDSS, expanded disability status scale; LYMPH, absolute lymphocyte count; NEUT, absolute neutrophil count; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PLT, platelets; post-HSCT, after hematopoietic stem cell transplant; PPMS, primary progressive multiple sclerosis; pre-HSCT, before hematopoietic stem cell transplants; RRMS, relapsing remitting multiple sclerosis; SII, systemic immune-inflammatory index; SPMS, secondary progressive multiple sclerosis; WBC, white blood cells.
[a]*p* value obtained with Mann–Whitney *U* test.
[b]*p* value with Chi-square test.

cohort, five patients had PPMS, 10 had RRMS, and six had SPMS. The pre-transplant EDSS scores were lower in the NR cohort compared with the R cohort, nonetheless this disparity was not statistically significant ($p = 0.069$).

3.2 | Clinical response to aHSCT

Thirty-seven patients experienced either a reduction or stabilization of their EDSS score after aHSCT in the R group, whereas 21 patients encountered a deterioration in their EDSS score in the NR group. The Chi-square test indicated that there was no statistically significant association between the type of MS and the response to aHSCT ($p = 0.232$). In the R group, the median EDSS score exhibited a decrease of 1 point, whereas in the NR group, it demonstrated an increase of 1.5 points.

3.3 | NLR, PLR, and SII index before and after aHSCT

CRP, neutrophils, platelets, and lymphocytes values were assessed prior to the transplantation procedure and exhibited no notable disparities between the R and NR groups (Table 1). The median pre-transplant NLR index was marginally elevated in the NR group, in contrast to the PLR and SII indexes, which were slightly higher in the R group. Nevertheless, as illustrated in Figure 1, no statistically significant disparity was observed. In comparison, the outcomes acquired from the CBC, 100 days after aHSCT indicated that the median of lymphocytes, NLR, PLR, and SII showed statistically significant difference between both groups. NLR in the R group was 1.8, whereas in the NR group it was 3.1 ($p = 0.003$) and PLR median was 194 in the R group and 295 in the NR group ($p = 0.024$). Furthermore, the SII index was 489.5 in the R group and 729.3 in the NR group ($p < 0.001$).

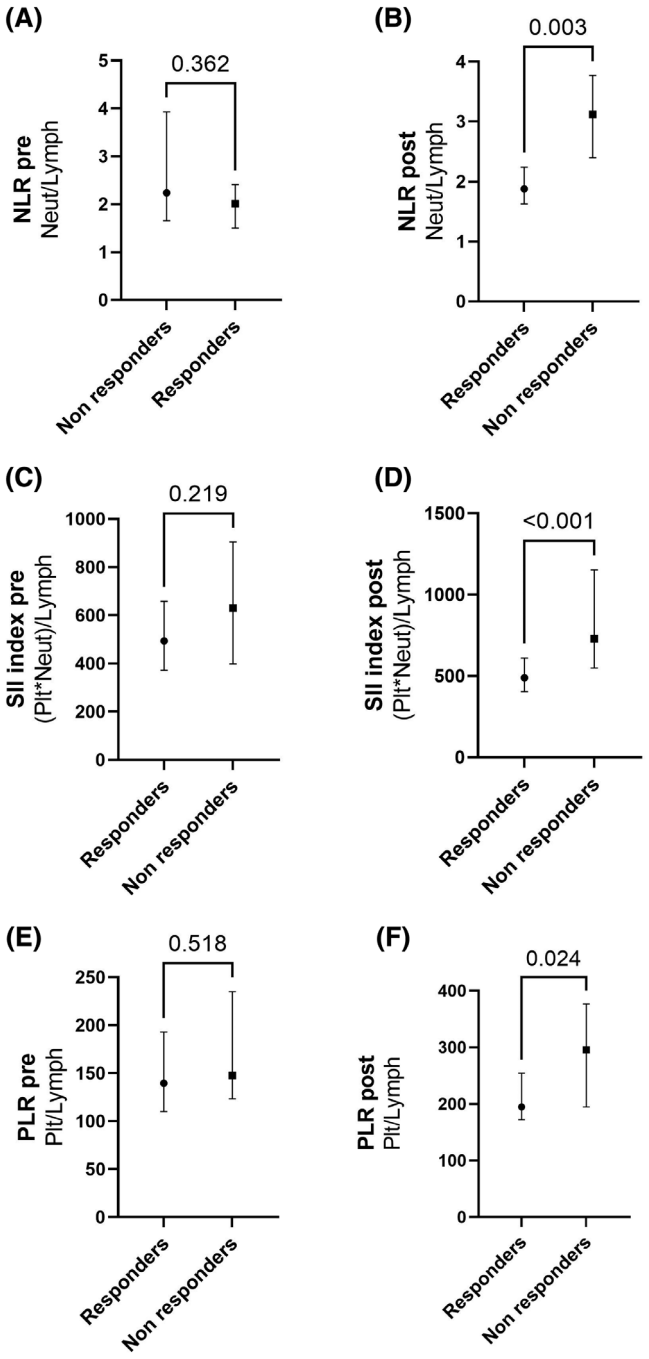

FIGURE 1 Changes in the neutrophil to lymphocyte ratio, systemic immune-inflammatory index, and platelet to lymphocyte ratio before and after the transplant. Among the response groups (A), (C), and (E), the values obtained prior to the autologous hematopoietic stem cell transplant (aHSCT) did not exhibit any statistically significant values for NLR, SII index, and PLR. On the other hand, when comparing the values obtained 100 days after aHSCT in groups (B), (D), and (F), a notable disparity was observed between these two groups. Lymph, absolute lymphocyte count; Neut, absolut neutrophil count; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Plt, platelets; post, after transplant; pre, before transplant; SII index, systemic immune-inflammatory index.

4 | DISCUSSION

In the current investigation, no association was observed between the NLR or any other biomarkers prior to aHSCT and the clinical manifestation of the disease, MS subtype, or any other clinical characteristic; therefore, these markers were found to have no predictive significance. However, after the transplantation procedure, the SII index, NLR, and PLR exhibited a statistically significant elevation in individuals who demonstrated an increase in their EDSS score 1 year after the treatment, in comparison with those persons who experienced an amelioration or stabilization of the neurological condition, as judged by changes in the EDSS score.

Neutrophils play a major role in inflammation. The increase of circulating neutrophils represents the immune system's response to mostly acute inflammation, although, less frequently, chronic inflammation also increases blood neutrophils.[28] In the USA, there has been established among the general population, an association of NLR with overall mortality to specific conditions, including acute and chronic kidney disease, cardiovascular disease, and pneumonia.[7,29] In multiple types of cancers, NLR has demonstrated to be an accurate marker of short and long-term mortality and survival after treatment.[30–32]

The research of neuro-autoimmune diseases has also benefited from NLR; it was found that NLR was significantly higher in persons with aquaporin 4 antibody neuromyelitis optica spectrum disorder (AQP-Ab NMOSD), myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD), autoimmune encephalitis (AIE), and Guillain–Barré Syndrome (GBS), than healthy controls.[10,11,33] Also, during an acute attack, patients with AQP-Ab NMOSD and MOGAD had higher NLR than when in remission.[10] Moreover, NLR was suggested as a useful progression marker in AIE and a predictor of response to treatment in GBS.[11,33] Previous studies demonstrated that NLR was significantly higher in MS patients than healthy controls and have suggested to be a useful marker for disease activity.[15,34]

SII index has been used mainly in the study of solid tumors. SII reflects the balance between the host inflammation and immune response status. In conditions where an unbalanced status is present, such as testicular cancer, hepatocellular carcinoma, and a wide spectrum of heart diseases, SII has been a reliable biomarker predicting outcomes, potential complications, and overall survival.[19–21] MS wise, SII index showed to be significantly higher in patients with active lesions in their MRI than those who did not showed active lesions.[35]

After HSCT, NLR, and PLR have been studied only in a context of hematological malignancies such as multiple myeloma, where the results were proved to have a prognostic value after the treatment and overall survival.[13,14] Unfortunately, there are no current studies comparing the relation between post-transplant NLR nor SII and the response to the HSCT in autoimmune diseases.

Our results showed elevated values in NR group for NLR, PLR, and SII at 100 days evaluation compared with the R group. This could suggest that the patients who did not showed a favorable response to transplantation could have a persistent inflammatory state after transplant that does not allow a disease stabilization. It has been shown

that even the immune reconstitution after HSCT could take more than 1 year,[36] the neutrophils become functionally competent after 2 months.[37,38] In Table 1 we can observe that there is no statistically significant difference in the absolute count of WBC, neutrophils, and platelets between the pre-transplant measurements and at 100 days follow up, this suggests that, although it has been reported that the use of cotrimoxazole and acyclovir could derive in neutropenia,[39] this prophylactic therapy did not have a great impact in the WBC count in our cohort. However, the absolute count of lymphocytes was lower at 100 days mainly in the NR group; the explanation for lymphopenia after 100 days of aHSCT may involve a combination of different factors like the delayed recovery of lymphocyte subsets or potential damage to lymphoid organs.

The plasma CRP levels before transplantation, as another marker of the acute phase response, did not present a significant difference between the response groups and the results were between the normal range. This result for CRP could be explained because the inflammatory state of the patients with MS may have become chronic as reported by Alatab et al. they found elevated CRP levels in MS patients even in the absence of acute attacks or infections.[40] However, CRP levels in our cohort were between the reference range (0–2.9 mg/L), which could mean that there is no association of CRP with MS. Unfortunately, the patients did not have an assessment of CRP levels after aHSCT which did not allow us to explore the possible usefulness of CRP levels as a biomarker in these patients.

The main limitation of our investigation pertains to the appraisal of CBC after aHSCT. Since all patients are of foreign origin, the outcomes were documented at the 100-day follow-up from diverse laboratories spanning various nations, which may engender incongruity in the findings. Additionally, the scope of the examined sample is restricted, possibly giving rise to a selection bias as we predominantly procure results from patients exhibiting satisfactory outcomes. The administration of cotrimoxazole and acyclovir as prophylactic therapy could influence the leukocyte levels; nonetheless, these medications are indispensable in the prevention of post-transplant infections.

5 | CONCLUSION

High NLR and SII index values after the aHSCT were associated with a worsening in the EDSS score. However, since this is the first ever study that compared NLR and SII index with the aHSCT response in persons with MS, further studies must be performed to corroborate this information.

AUTHOR CONTRIBUTIONS

Guillermo Ocaña-Ramm: Conceptualization; data curation; investigation; writing–original draft preparation. **Moisés Manuel Gallardo-Pérez:** Conceptualization; data curation; methodology; formal analysis; writing–review & editing. **Solón Javier Garcés-Eisele:** Methodology; formal analysis; writing–review & editing. **Daniela Sánchez-Bonilla:** Investigation. **Max Robles-Nasta:** Investigation. **Edgar Jared Hernández-Flores:** Investigation. **Luis Enrique Hamilton-Avilés:** Investigation. **Paola Negrete-Rodríguez:** Investigation. **Miranda Melgar-de-la-Paz:** Investigation. **Olivia Lira-Lara:** Investigation. **Juan Carlos Olivares-Gazca:** Investigation. **Guillermo J Ruiz-Delgado:** Investigation. **Guillermo J Ruiz-Argüelles:** Supervision; writing–review & editing.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Ocaña-Ramm G, Gallardo-Pérez MM, Garcés-Eisele SJ, et al. Neutrophil to lymphocyte ratio and systemic immune-inflammatory index as markers of response to autologous hematopoietic stem cell transplantation in persons with multiple sclerosis. *Int J Lab Hematol*. 2024;1-7. doi:10.1111/ijlh.14259