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Evaluation of the Neutrophil to Lymphocyte Ratio and Monocyte to Lymphocyte Ratio in Patients with Multiple Myeloma

Izeta Aganović-Mušinović[1], Alma Sofo-Hafizović[2], Maida Rakanovć-Todić[3], Sanita Maleškić Kapo[3], Sabina Mahmutović-Vranić[4], Mirela Mačkić-Đurović[5], Amela Dervišević[6], Lejla Burnazović-Ristić[3]

[1]*Department of Immunology, University of Sarajevo – Medical Faculty, Sarajevo, Bosnia and Herzegovina*
[2]*Clinic for Hematology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina*
[3]*Department of Pharmacology, Toxicology and Clinical Pharmacology, University of Sarajevo – Medical Faculty, Sarajevo, Bosnia and Herzegovina*
[4]*Department of Microbiology, University of Sarajevo – Medical Faculty, Sarajevo, Bosnia and Herzegovina*
[5]*Center for Genetics, University of Sarajevo – Medical Faculty, Sarajevo, Bosnia and Herzegovina*
[6]*Department of Physiology, University of Sarajevo – Medical Faculty, Sarajevo, Bosnia and Herzegovina*

Abstract : Neutrophil to lymphocyte ratio (NLR) and monocyte to lymphocyte ratio (MLR) seem most valuable parameters to predict the prognosis of patients with malignant tumors. The aim of the study is to evaluate the NLR and MLR in MM patients. Data from 90 MM patients randomized into three groups were collected. After white blood cell (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and absolute monocyte count (AMC) were obtained, NLR and MLR was calculated. A p-value < 0.05 was considered statistically significant. **S**tatistically lower value of AMC and in MLR were found between genders. Our results show the elevated ALC in stage III MM patients compared to those in stage II (p=0.04) and in NLR on in ISS stage III MM patients compared to stage II (p=0.049). The same variables used in comparation between MM patients at different disease stages groups showed significant difference in ANC in MM patients in relapse stage in regard to those in remission stage group (p=0.013), as well as in MLR in MM patients in relapse stage group in regard to those newly diagnosed MM patients (p=0.01). The ALC to AMC ratio serves as a prognostic immune biomarker in newly diagnosed MM patients and can reflect the strength of the host immune system to tumor-induced immune dysfunction. Additionally, NLR and MLR can be used as diagnostic markers for MM patients, with higher NLR indicating a pro-tumor inflammatory condition that can lead to tumor progression and poorer prognosis.

Keywords: *multiple myeloma, neutrophile, lympocyte, monocyt*

I. INTRODUCTION

Multiple myeloma (MM) is a malignant tumor of bone marrow with appearance of many plasma cells that produce single paraprotein. Plasma cells suppress other immune cells in bone marrow due to what the patient face with lack or reduced number of white blood cells and red blood cells. Cells of the monocyte lineage are crucial to the innate immune response. Their main function is to serve as the first line of resistance against

microbes, but also to activate adaptive immune responses. There are two types of immunological responses: immune response-1 and immune response-2, of which the second one is prognostically unfavorable in malignant tumors. Many genes, whose products take part in immunologic response-2 are expressed by peripheral blood monocytes. There is an association between their expression level and cancer proliferation. MM cells cannot simply displace hematopoietic cells upon BM infiltration but rather selectively modulate the BM microenvironment. Additionally, monocyte chemoattractant protein plays important role in modulating tumorigenesis [1,2].

Although novel therapeutic measures, such as steroids, chemotherapy, thalidomide or lenalidomide and stem cell transplant have been developed to yield improved clinical outcomes, the relapse rate and mortality remain high and the prognosis of MM is also highly heterogeneous [3]. Thus, the accurate and rapid prediction of disease prognosis is essential for treatment planning.

Inflammatory cells in tumor microenvironments induce the proliferation and survival of cancer cells, promote angiogenesis and metastasis, and depress antitumor immunity [4], and inflammatory factors in clinical practice may be more easily and cost effectively detected. Inflammation is one of the hallmarks of cancer and tumor-associated inflammatory response has a critical role in enhancing tumorigenesis by inducing tumor cell growth, angiogenesis and genome instability [5]. Neutrophils and lymphocytes are regarded as cardinal cells closely correlated with local inflammation and immune responses [6].

Complete blood count (CBC) is an inexpensive and easy to perform diagnostic test, widely used in everyday clinical practice. It is of great importance in diagnostics and monitoring of different medical conditions, not only hematological ones. Although used for years, new applications of CBC are still being discovered. Recently, numerous studies focused on proportion of different types of leukocytes in various medical conditions. Neutrophil to lymphocyte ratio (NLR) and monocyte to lymphocyte ratio (MLR) seem most valuable parameters [7]. Neutrophil-to-lymphocyte ratio (NLR) indicates the balance between pro-tumor and anti-tumor status and thus a useful index to predict the prognosis of patients with malignant tumors.

Neutrophils exhibit anti-tumor activity, but also suppress the cytolytic activity of immune cells such as lymphocytes [8]. High NLR reflects a decrease in the number of lymphocytes and an elevated number of neutrophils in tumor microenvironment. The MLR is calculated by dividing the absolute monocyte counts by the absolute lymphocyte counts from the blood test. The absolute neutrophil count might serve as a marker of systemic inflammation, which provides favorable environment for the development of malignant tumors. In contrast, the absolute lymphocyte count reflects immunosuppression, which is associated with poor outcome in a number of solid and hematological malignancies [9]. Therefore, we have decided to evaluate the NLR as well as MLR in MM patients grouped either through MM International Staging System or through Salomon-Durie classification.

II. MATERIALS AND METHOD

2.1. Patients

All adult patients who were diagnosed with MM and went to Clinical University Center of Sarajevo as an outpatient and/or inpatient were included in this study. Patients who entered the study had to meet several criteria: to have monoclonal plasma cells in the bone marrow, to have monoclonal protein present in the serum and/or urine and to have evidence of lytic bone lesions. Exclusion criteria for this study were: previous or comitant other malignancies, primary or secondary thrombocytopenia and chronic anti-inflammatory medication users. In this retrospective study we have used data from 90 MM patients who were divided into three groups: patients who were newly diagnosed; those at steady state of MM and those who were in relapse state - 30 patients in each group. On the other hand, all of them have been classified by MM International Staging System (ISS), using relevant parameters to do so.

2.2. Methods

White blood cell (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and absolute monocyte count (AMC) obtained by Sysmex XN-9000/5000. The NLR was calculated as the ratio between absolute neutrophil count and absolute lymphocyte count. MLR was calculated as the ratio between absolute monocyte count and absolute lymphocyte count.

2.3. Statistical analysis

SPSS (Statistical Package for Social Science Inc., Chicago, IL, USA) version 13.0 for Windows was used for statistical analysis. Normality of continuous data was determined by the Shapiro - Wilk or Kruskal-Wallis test depending on the sample size.

Data are presented as number of cases (n) and as frequencies (%) for categorical variables, as mean ± standard deviation (SD) for normally distributed variables, or as median and interquartile ranges for skewed variables. The independent Student's t-test is used to analyze the difference of means between two groups. ANOVA test followed by post-hoc Scheffe test or Kruskal-Wallis test followed by Man-Whitney test were used to compare the differences between more than two groups, as appropriate.

To determinate the accuracy and respective best cut-off values of the parameters for differentiation between newly diagnosed patients with multiple myeloma and patients in relapse stage, the Receiver Operating Characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used. ROC curves' accuracy rate was calculated with a 95% Confidence Interval (95% CI). A p-value < 0.05 was considered statistically significant.

III. RESULTS

Table 1. Baseline characteristics of the study participants

Variables		All cases (n=90)
Age (years)		59.0 (54.0 – 62.3)
Gender	Male	42 (46.7%)
	Female	48 (53.3%)
ISS	I	7 (7.8%)
	II	23 (25.6%)
	III	60 (66.6%)
Absolute neutrophil count ($\times 10^9$)		2.8 (2.2 – 4.0)
Absolute lymphocyte count ($\times 10^9$)		1.3 (1.0 – 2.0)
Absolute leukocyte count ($\times 10^9$)		5.4 (4.3 – 7.1)
Absolute monocyte count ($\times 10^9$)		0.5 (0.4 – 0.7)
NLR		2.1 (1.4 – 3.5)
MLR		0.4 (0.3 – 0.6)

Data are shown as: number (%) or mean (±SD) or as median (range). ISS - International Staging System. NLR - Neutrophil-to-Lymphocyte Ratio. MLR - Monocyte-to-Lymphocyte Ratio.

Table 2. Baseline characteristics of the study participantsgrouped by gender

Variables		Male (n=42)	Female (n=48)	p
Age (years)		60.0 (53.8 – 63.3)	59.0 (55.0 – 62.0)	0.370
ISS	I	1 (2.4%)	6 (12.5)	0.31
	II	13 (31%)	10 (20.8)	
	III	28 (66.6%)	32 (66.7)	
Absolute neutrophil count ($\times 10^9$)		3.1 (2.2 – 3.9)	2.6 (2.1 – 4.3)	0.563
Absolute lymphocyte count ($\times 10^9$)		1.3 (1.1 – 1.8)	1.4 (1.0 – 2.2)	0.771
Absolute leukocyte count ($\times 10^9$)		6.0 ± 2.2	5.6 ± 2.0	0.330
Absolute monocyte count ($\times 10^9$)		0.6 (0.5 – 0.8)	0.5 (0.3 – 0.6)	**0.002**
NLR		2.1 (1.3 – 3.4)	2.2 (1.5 – 3.9)	0.818
MLR		0.41 (0.34 – 0.62)	0.3 (0.3 – 0.52)	**0.016**

Data are shown as number (n), or percentage (%), or mean (±SD) or median (range). ISS - International Staging System. NLR - Neutrophil-to-Lymphocyte Ratio. MLR - Monocyte-to-Lymphocyte Ratio.

Table 3. Comparation of absolute neutrophil count, absolute lymphocyte count, absolute leukocyte count, absolute monocyte count, NLR, MLR and LMR between MM patients grouped by ISS

Variables	ISS Stage I (n=7)	ISS Stage II (n=23)	ISS Stage III (n=60)
Absolute neutrophil count ($\times 10^9$)	3.6 (2.6 – 6.0)	3.1 (2.3 – 4.0)	2.7 (2.1 – 3.9)
Absolute lymphocyte count ($\times 10^9$)	1.9 ± 0.7	2.0 ± 1.0	1.4 ± 0.6
Absolute leukocyte count ($\times 10^9$)	7.0 (5.2 – 8.5)	6.4 (5.0 – 7.8)	5.1▲ (3.9 – 6.3)
Absolute monocyte count ($\times 10^9$)	0.5 (0.4 – 0.6)	0.6 (0.5 – 0.7)	0.5 (0.4 – 0.7)
NLR	2.2 (1.5 – 3.4)	1.5 (1.1 – 3.6)	2.2▲▲ (1.5 – 3.9)
MLR	0.31 (0.2 – 0.43)	0.34 (0.27 – 0.49)	0.40 (0.25 – 0.62)
LMR	3.2 (2.3 – 5.1)	2.9 (2.1 – 3.7)	2.5 (1.6 – 4.1)

Data are shown as mean (±SD) or median (range). NLR - Neutrophil-to-Lymphocyte Ratio. MLR - Monocyte-to- Lymphocyte Ratio. LMR - Lymphocyte-to- Monocyte Ratio. ISS - International Staging System. ▲p=0.04 compare to ISS Stage II. ▲▲p=0.049 compare to ISS Stage II.

Table 4. Comparation of absolute neutrophil count, absolute lymphocyte count, absolute leukocyte count, absolute monocyte count, NLR, MLR and LMR between MM patients at different disease stages groups

Variables	Newly diagnosed group (n=30)	Remission stage group (n=29)	Relapse stage group (n=31)
Absolute neutrophil count ($\times 10^9$)	3.1 (2.3 – 4.6)	3.6 (2.6 – 4.1)	2.6• (1.8 – 3.5)
Absolute lymphocyte count ($\times 10^9$)	1.6 (1.1 – 2.3)	1.3 (1.0 – 1.9)	1.3 (0.7 – 1.7)
Absolute leukocyte count ($\times 10^9$)	5.6 (4.8 – 7.4)	6.0 (4.8 – 7.0)	4.6 (3.6 – 7.8)
Absolute monocyte count ($\times 10^9$)	0.5 (0.4 – 0.6)	0.5 (0.47 – 0.7)	0.6 (0.3 – 0.8)
NLR	1.7 (1.2 – 3.6)	2.6 (1.6 – 3.8)	1.8 (1.3 – 3.4)
MLR	0.29 (0.23 – 0.42)	0.38 (0.22 – 0.64)	0.41•• (0.31 – 0.67)

Data are shown as median (range). NLR - Neutrophil-to-Lymphocyte Ratio. MLR - Monocyte-to- Lymphocyte Ratio.LMR - Lymphocyte-to-Monocyte Ratio. •p=0.013 compare to Remission stage group. ••p=0.01 compare to Newly diagnosed group.

Table 5. Optimal *cut-off*, area under the curve with 95% confidence interval (AUC, 95% CI), sensitivity, specificity, positive and negative predictive value, overall accuracy of NLR, MLR and LMR in differencing between newly diagnosed patients with multiple myeloma and patients in relapse stage

	Optimal cut-off	AUC (95% CI)	SEN (%)	SPE (%)	p
NLR	1.46	0.487 (0.340 - 0.634)	70	35.5	0.863
MLR	0.295	0.684 (0.548 - 0.820)	83.9	53.3	**0.013**
LMR	3.355	0.688 (0.552 - 0.823)	56.7	80.6	**0.012**

AUC - Area under the curve. CI - Confidence Interval. SEN - sensitivity. SPE - specificity. NLR - Neutrophil-to-Lymphocyte Ratio. MLR - Monocyte-to-Lymphocyte Ratio. LMR - Lymphocyte-to-Monocyte Ratio. p – probability.

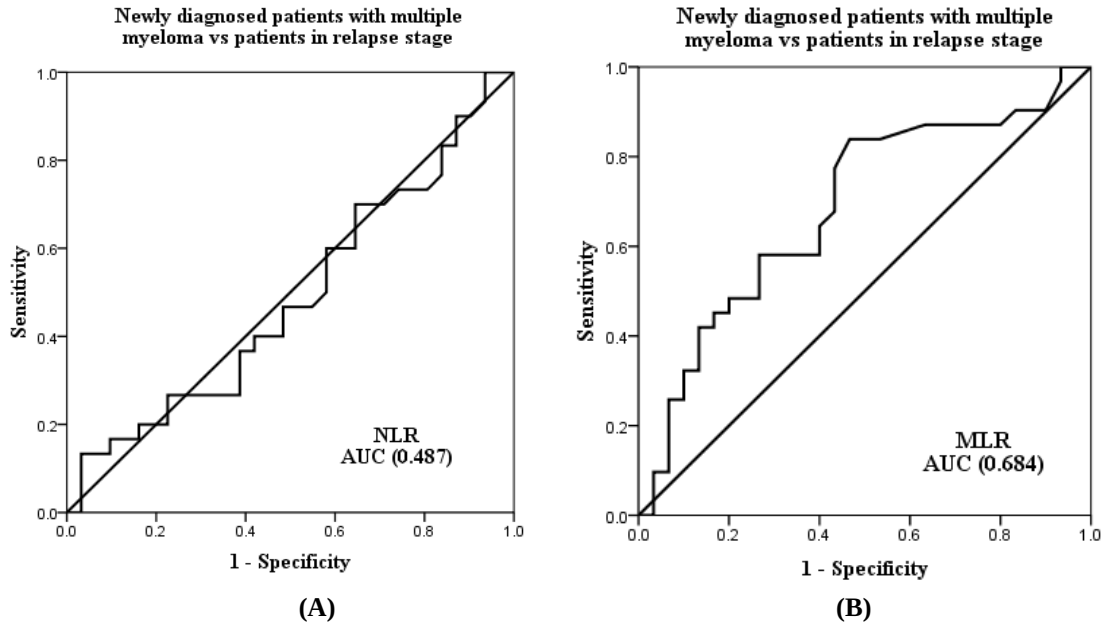

Figure 1.(A) Receiver operating characteristic (ROC) curve of NLR for differentiation between newly diagnosed patients with multiple myeloma and patients in relapse stage. (B) Receiver operating characteristic (ROC) curve of MLR for differentiation between newly diagnosed patients with multiple myeloma and patients in relapse stage.

IV. DISCUSSION

Monocytes play an important role in tumor microenvironment and might be considered as markers of a prolific tumor burden. There are two types of macrophages activation: M1 and M2 activation, depending on the type of stimulation. M1 activation is stimulated by lipopolysaccharide and IFN-γ. M1 macrophages infiltrate the tumor microenvironment in response to inflammatory signals mentioned above and release proinflammatory cytokines and chemokines, which promote the differentiation of T and NK cells. Macrophages can differentiate into a tumor-associated macrophages (TAMs) [10]. TAMs influence tumor cells as well as the tumor microenvironment. TAMs stimulate tumor cells proliferation, migration and genetic instability and promote angiogenesis and lymphoangiogenesis, which facilitates metastasis [10,11]. The absolute lymphocyte count (ALC) to the absolute monocyte count (AMC) ratio in the peripheral blood (PB) serves as a powerful prognostic immune biomarker in newly diagnosed MM patients and may reflect the immunologic status of these patients. Among the BM cells implicated in this process are tumor-associated macrophages (TAMs) [12]. These are derived from circulating monocytes and create an immunosuppressive microenvironment that promotes the growth and survival of MM cells [12,13].

The ratio of ALC to AMC may represent the relative strength of the host immune system (that is, ALC) to tumor-induced immune dysfunction (that is, AMC, reflective of TAMs). The ALC/ AMC ratio can serve as a better prognostic immune biomarker in newly diagnosed MM than ALC or AMC alone. Accordingly, we investigated ALC, AMC and AMC/ALC at diagnosis, in remission stage and in relaps stage of MM patients.

In this study, we have found statistically lower value of absolute monocytes count and in monocyte to lymphocyte ratio, between genders, but not regarding to ISS system of classification (Table 2). The baseline characteristics of the study participants were presented in Table 1.

Systemic inflammation response from malignant cells can cause immune suppression by which tumor cells can escape from host immune reaction [14]. Second, many types of tumor tissues are infiltrated by neutrophils. Tumor-associated neutrophils are related to progress in cancer for they are the primary source of circulating vascular endothelial growth factor (VEGF), which can accelerate tumor-related angiogenesis [15,16]. Neutrophils directly help tumor cells survive by inducing proliferation [17]. Therefore, increased NLR, caused by an increase in the number of neutrophils and a decrease in lymphocyte count, indicates that the balance between pro-tumor and anti-tumor status has been disrupted and skewed to a pro-tumor inflammatory condition, which leads to tumor progress and poor prognosis.

While the benefits of neutrophil actions are undeniable in the context of infection or trauma, their effects in the context of oncogenesis seem problematic [18].

When we have compared the absolute neutrophil count, absolute leukocyte count, absolute monocyte count, NLR and MLR between MM patients grouped by ISS system of classification, we noticed the elevated absolute leukocytes count in stage III MM patients compare to those in stage II ($p=0.04$) and in neutrophil to lymphocyte ration in ISS stage III MM patients compare to stage II ($p=0.049$).

The same variables used in comparation between MM patients at different disease stages groups showed significant difference in absolute neutrophil value in MM patients in relapse stage in regard to those in remission stage group ($p=0.013$), as well as in MLR in MM patients in relapse stage group in regard to those newly diagnosed MM patients ($p=0.01$) (Table 4).

The optimal cut-off level for NLR was 1.46 with sensitivity of 70%, specificity of 35.5% (area under the curve (AUC): 0.487; $p=0.863$). The ROC analysis also suggested 0.295 as optimal cut-off points for MLR (sensitivity of 83.9%, specificity of 83.3%, AUC: 0.684; $p=0.013$) in differentiating newly diagnosed patients with multiple myeloma and patients in relapse stage (Table 5; Figure 1).

Hanahan and Weinberg (2011) hypothesized the possible hypothesis regarding pathophysiology is the tumor-associated inflammatory response, which is now considered as one of hallmarks of cancer. Inflammation does indeed appear to play a role from the very earliest to the advanced stages of cancer [5].

As a hallmark of cancer, inflammation factors lead to angiogenesis, inhibition of apoptosis, and DNA damage [19,20], which then promote cancer and affect host immunity as well as tumor response to treatment [21,22]. NLR was a representative factor of systematic inflammation. A high NLR means a relatively elevated neutrophil count and depletion of lymphocytes, which can change the tumor microenvironment and facilitate tumor invasion and metastasis by secreting serum vascular endothelial growth factor and various proteases [23]. On the other hand, depletion of lymphocytes means weakened antitumor immunity and therefore promote tumor proliferation. Furthermore, pretreatment lymphopenia greatly increased the incidence of severe bacterial infection for MM patients [24].

Findings of Romano et al. (2017) confirm the results of Dosani et al. (2017) and indicate that NLR and LMR could have a different biological meaning since they do not correlate each other and have a prognostic value in different subpopulation of patients [25,26]. This difference is probably linked to the different role of neutrophils and monocytes in the complex network of the bone marrow microenvironment that supports myeloma growth and is further supported by the finding that neutrophils and monocytes counts are independent prognostic factors in multivariate analysis.

V. CONCLUSION

Monocytes play a crucial role in the tumor microenvironment and can serve as markers of a prolific tumor burden. Macrophages can differentiate into TAMs, which promote tumor growth, migration, and survival. The ALC to AMC ratio serves as a prognostic immune biomarker in newly diagnosed MM patients and can reflect the strength of the host immune system to tumor-induced immune dysfunction. Additionally, NLR and MLR can be used as diagnostic markers for MM patients, with higher NLR indicating a pro-tumor inflammatory condition that can lead to tumor progression and poorer prognosis. Inflammation is considered a hallmark of cancer, promoting angiogenesis, inhibition of apoptosis, and DNA damage, which affects host immunity and tumor response to treatment.

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