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## ORIGINAL PAPER

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# NEUTROPHIL/LYMPHOCYTE RATIO AND PLATELET/LYMPHOCYTE RATIO IN PATIENTS WITH NSCLC

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## ABSTRACT

**Objective:** to compare neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in patients with NSCLC (Non-Small-Cell Lung Cancer) with and without metastases at the time of diagnosis to find out if there is the importance of these cell ratios in the assessment of severity NSCLC. **Material and Methods:** this is the retrospective analysis of NLR and PLR in patients with NSCLC at the time of the diagnosis of disease before any anti tumor treatment (chemotherapy, radiotherapy, surgery). 57 of patients with NSCLC treated in the first three months of 2016 .year were chosen at random regardless of sex and age. We examined full blood count cells (FBC), calculated NLR and PLR in every patient and compared obtained values in patients with and patients without metastases. **Results:** In 57 patients with NSCLC there were 15 males with metastases, 28 without metastases, and 8 females with metastases, 6 without metastases. Since there was no regularity in the distribution of obtained values of NLR and PLR we made the Mann-Whitney U test. Mean values are presented with a median and interquartile percentiles. There was no significant difference in NLR between patients without and with metastases ( $p = 0.614$ ;  $p = NS$ ) as well as in PLR ( $p = 0.068$ ;  $p = NS$ ). **Conclusion:** There must be a link between the immune status of the organism and lung cancer development. Immune cells have become of interest in recent years and much work has been done to study their role in the genesis of cancer but it did not give satisfactory results. Further clinical studies on large number of patients and further laboratory examination of the role of immune cells in cancer development and suppression are required.

**Key words:** NSCLC, NLR, PLR.

## 1. INTRODUCTION

NSCLC is the most common type of lung cancer and the most common malignant neoplasm worldwide (1). During past decades, various studies have attempted to identify molecular biomarkers to predict the prognosis of NSCLC (2, 3). Numerous promising biomarkers have been evaluated but none of these have been effective for clinical use (2, 3). Recently the role of immune cells in cancer has become of increasing interest.

Lymphocytes, macrophages and granulocytes are involved in the anti-cancer battle. The main cell population in anti-cancer immune response is the population of cytotoxic T lymphocytes (CTLs) (4). The CTLs population is represented by CD8+ lymphocytes, CD4+ lymphocytes, natural killer cells (NK), natural killer T cells (NKT) and lymphocytes B (5, 6). Cancer cells are killed by induction of apoptosis by cytolytic reaction or membrane-receptor induction of programmed death. The successful cytotoxic attack needs an

effective antigen presentation by tumor cells and antigen presenting cells (APC). This is achieved by macrophages and dendritic cells (DCs) (7).

Anti-cancer defense is ineffective in clinically detectable cancers and the greater is the size of a tumor mass, the less effective anti-cancer response is (8). Lung cancer cells hide against cytotoxic attack by low antigen presentation and low co-stimulatory molecule expression. The lung cancer antigens are unstable and badly defined as a result of multiple genetic and epigenetic alterations during oncogenesis (9).

Neutrophils play a key role in protection against microbial infections and in inflammation. Chronic inflammation is associated with increased susceptibility for cancer. Hepatitis B (10) and inflammatory bowel disease (11) are examples, leading to hepatocellular and colorectal cancer. Neutrophils, as a key component in inflammation, may play a crucial role in inflammation driven tumorigenesis (12). Neutrophils support angiogenesis via secretion of proangiogenic fac-

tors or by proteolytic activation of proangiogenic factors. Neutrophils are implicated in tumor growth through the proteolytic release of EGF-epidermal growth factor, TGFβ1-transforming growth factor – β1, and PDGF – platelet derived growth factors from the extracellular matrix (ECM) (13). Neutrophils recruit other tumor promoting cells. Immature neutrophils or G-MDSC (granulocytic myeloid derived suppressor cells) are implicated in the establishment of an immunosuppressive tumor microenvironment. Neutrophils kill tumor cells through direct or antibody dependent cell cytotoxicity (ADCC) (13). They accumulate in large numbers in premetastatic organs and have a positive effect on tumor cell seeding (14-17). Also, it has been shown that neutrophils limit metastatic seeding by killing tumor cells (14, 16).

Neutrophils do not affect the growth of the metastatic nodules (14, 16). There is a “polarization” of neutrophils in tumor promoting and antitumor phenotype which is mediated via cytokines in the tumor microenvironment (i.e. TGFβ1 and IFNs). Neutrophils consist of pro- and antitumor subpopulations (17). Neutrophil abundance correlates with a better prognosis in some studies and a worse prognosis in others (18).

Platelets play a significant role in cancer growth, progression and metastasis (19, 20). Significant attention has been given to the association between malignancies and coagulation (19, 20). A hypercoagulability is one of the signs of a more aggressive disease and thromboembolism is one of the major causes of mortality in cancer (21). A prognostic significance between the platelet count and lung cancer has been identified but not fully elucidated (22-27). Platelets release some growth factors such as platelet-derived growth factor, platelet factor 4, and thrombospondin which promote hematogenous tumor spread, tumor cell adhesion, invasion and angiogenesis and play an important role in tumor progression (22, 25-27).

Platelets contain many active molecules and, as they adhere to sites of tumor activated or injured endothelium; many of these molecules are released into the local microenvironment leading to platelet-mediated effects on vascular tone and neo-angiogenesis (22-27). Platelets play important roles in the tumor microenvironment that may be thought of as “a wound that never heals” (28).

**2. OBJECTIVE**

Objective of this study is to compare neutrophil/ lymphocyte ratio (NLR) and platelet /lymphocyte ratio (PLR) in patients with NSCLC (Non- Small- Cell Lung Cancer) with and without metastases at the time of diagnosis to find out if there is the importance of these cell ratios in the assessment of severity NSCLC.

**3. MATERIAL AND METHODS**

This is the retrospective analysis of NRL and PRL in patients with NSCLC at the time of the diagnosis of disease before any anti tumor treatment (chemotherapy, radiotherapy, surgery). 57 of patients with NSCLC treated in the first three months of 2016 .year were chosen at random regardless of sex and age. We examined full blood count cells (FBC – n x 10<sup>9</sup>/ L), calculated NLR and PLR in every patient and compared obtained values in patients with metastases and patients without metastases.

**4. RESULTS**

In 57 patients there were 15 males (26%) mean aged 68, 64 with metastases, 28 males (49%) mean aged 64,63 years without metastases, 8 females (14%) mean aged 61,63 with metastases and 6 females (11%) mean aged 63,33 years without metastases.

There were 23 patients with NSCLC (40%) with metastases and 34 patients (60%) without metastases. The values of NLR in 34 patients without metastases were: 5,15; 8,57; 1,81; 1,45; 1,69; 3,77; 1,35; 1,83; 1,77; 2,11; 1,65; 2,26; 2,78; 4,25; 3,52; 1,92; 1,37; 1,77; 3,52; 1,22; 3,92; 3,28; 1,47; 3,74; 3,74; 1,82; 3,68; 2,39; 2,39; 2,67; 1,88; 1,70; 4,14; 2,84. The values of NLR in 23

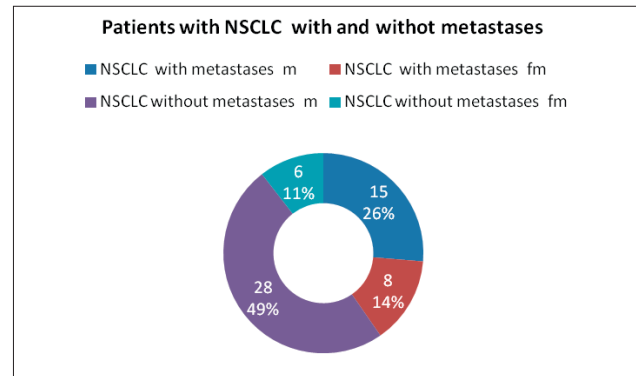


Figure 1. NSCLC with and without metastases in males and females

patients with metastases were: 1,51; 13,3; 0,58; 2,25; 1,71; 3,94; 2,47; 2,97; 2,58; 2,35; 2,35; 2,01; 4,46; 4,47; 3,23; 0,78; 2,79; 2,39; 3,67; 2,23; 2,25; 6,54; 1,56; (Figure 2)

NLR in patients without metastases = 2.32 (1.75 to 3.69), in patients with metastases= 2.39 (2.01- 3.67). The values of PLR in 34 patients without metastases were: 221,85; 261,0 ; 115,34; 69,8; 130,0; 166,9; 78,93; 50,29; 105,98; 137,99; 70,77; 106,9; 178,78; 168,4; 123,7; 72,5; 150,54; 83,02; 156,46; 76,12; 184,62; 156,46; 93,85; 225,78; 225,78; 68,09; 281,58; 105,56; 105,56; 116,94; 68,46; 92,71; 328,79; 107,69. The values of PLR in 23 patients with metastases were: 82,49; 402,56; 172,07;

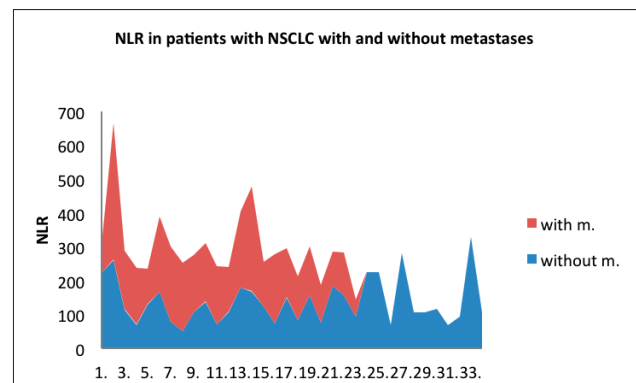


Figure 2. NRL in patients with NSCLC

167,60; 104,96; 220,53; 220,81; 201,15; 168; 171,65; 171,85; 133,09; 225,78; 307,84; 131,80; 204,90; 143,30; 128; 142,67; 110,90; 100,30; 124,60; 49,83. (Figure 3).

PLR in patients without metastases = 116.14 (81.99 to 170.99), in patients with metastases=167.60 (124, 60-204.90). Since there was no regularity in the distribution of obtained values of NLR and PLR we made the Mann-Whitney U test. Mean values are not presented using the

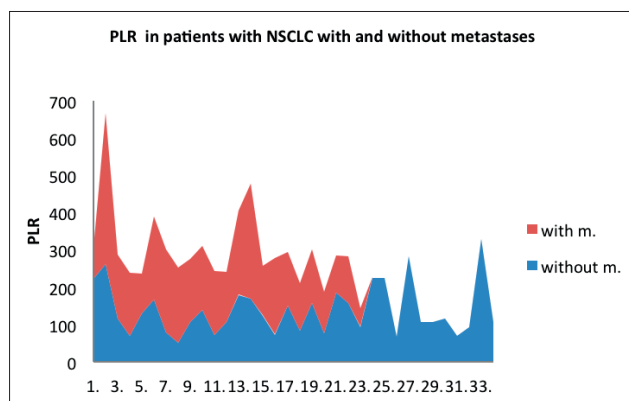


Figure 3.

X and SD, but with a median and interquartile percentiles. The NLR in patients with NSCLC without metastases amounted to 2.32 (1.75 to 3.69) and was not significantly different from the NLR in patients with metastases 2.39 (2.01- 3.67) ( $p=0.614$ ;  $p=NS$ ). The PLR in patients with NSCLC without metastases amounted to 116.14 (81.99 to 170.99) and was not significantly different from the PLR in patients with metastases 167.60 (124, 60- 204.90) ( $p = 0.068$ ;  $p = NS$ ).

## 5. DISCUSSION

Various studies have attempted to identify molecular biomarkers to predict the prognosis of NSCLC (2, 3). Recently the role of immune cells in cancer has become of increasing interest.

Lymphocytes, macrophages and granulocytes are involved in the anti-cancer battle (1-8). The main cell population in anti-cancer immune response is the population of cytotoxic T lymphocytes (CTLs) (4). Neutrophils may play a crucial role in inflammation driven tumorigenesis (12). Neutrophil population consists of pro- and antitumor subpopulations (17). Neutrophil abundance correlates with a better prognosis in some studies but a worse prognosis in others (18). Platelets release some tumor growth factors which play a significant role in cancer growth, progression and metastasizing (19, 20, 22, 25-28).

Elevated pretreatment NLR, PLR and mean platelet volume (MPV) in peripheral blood were identified as independent prognostic factors associated with poor survival with various cancers including NSCLC (29). In 81 patients with lung cancer NLR and PLR values were significantly higher compared to the healthy subjects (NLR: 4.42 vs 2.45  $p=0.001$ , PLR: 245.1 vs 148.2  $p=0.002$ ). MPV values were similar in both groups (7.7 vs 7.8). No significant relationship was determined between these markers and histopathology or TNM stages (29).

Pretreatment high NLR and PLR were associated with significantly shorter disease-free and survival rates in study worked on 94 patients with NSCLC; there was not impact on the response to chemoradiotherapy (30).

In 149 patients with NSCLC the pretreatment PLR is correlated with clinical outcomes after stereotactic radiation. There was no correlation between NLR and nonlocal failure. PLR was associated with freedom from nonlocal failure. Nonlocal failure rates were 11% for patients with PLR less than 250 and 58% for PLR greater than 250 ( $p < 0.001$ ).

Patients with high pretreatment PLR had shorter survival after stereotactic radiotherapy (31).

Some studies indicated that the combination of NLR and PLR could be a better prognostic factor. In study on 366 patients in III and IV stage of NSCLC, patients could be divided into three prognostic groups prior to treatment: poor:  $NLR > 2.68$ ; moderate:  $NLR \leq 2.68$  and  $PLR > 119.50$ ; and good:  $NLR \leq 2.68$  and  $PLR \leq 119.50$  (32).

A high pretreatment PLR (33) and NLR (34) might be a predictive factor of poor prognosis in NSCLC—a shorter survival after treatment.

Some authors (35) failed to find the prognostic significance of NLR in NSCLC and some (36) did not find correlation between PLR and prognosis of NSCLC.

We compared NLR and PLR in patients with NSCLC without and with metastases at the time of the diagnosis of diseases. Fact is that presence of metastases showed the further stadium of illness. We wanted to show if these cell ratios were different in these two groups. NLR in patients without metastases was 2.32 and PLR 116.14; in patients with metastases NLR was 2.39 and PLR 167.60. NLR and PLR were higher in patients with metastases but not significantly. Although there was not statistical significance these results show that NLR and PLR could be useful in preliminary assessment of NSCLC before any treatment. They can be useful predictors for worse prognosis but we still do not know reference values. If our sample were greater we might be given statistical significant results.

## 6. CONCLUSION

Immune cells and their ratio influence prognosis and that could be clinically applied in NSCLC. An incomplete understanding of the role of immune cells in lung cancer still remains. More investigations will improve the understanding of the lung cancer and may develop novel therapeutic opportunities. NLR and PLR before treatment may be useful biomarkers in NSCLC patients. Larger prospective studies are required to confirm these findings.

• Conflict of interest: none declared.

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