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

Vesna Cukic

Clinic for Pulmonary Diseases and TB “Podhrastovi”, Clinical centre of Sarajevo University, Bosnia and Herzegovina

Corresponding author: Vesna Cukic, MD, PhD. Bjelave 99, Sarajevo, Phone number;+387 61 480 228.
E-mail: vesna-cukic @ hotmail.com

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 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), 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 NLR 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 10^9/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 patients with and without metastases were: 1,51; 13,3; 0,58; 2,25; 1,71; 3,94; 2,47; 2,97; 2,58; 2,35; 3,25; 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 was 2.32 (1.75 to 3.69), in patients with metastases was 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 1. NSCLC with and without metastases in males and females

Figure 2. NLR in patients with and without metastases

NLR in patients with NSCLC

| NLR | with metastases | without metastases |
|-----|----------------|--------------------|
| 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. Platelet/Lymphocyte Ratio in Patients with NSCLC

Patients with NSCLC with and without metastases

- NSCLC with metastases
- NSCLC without metastases

| PLR | with metastases | without metastases |
|-----|----------------|--------------------|
| 68,09 | 281,58 | 105,56 |
| 116,94 | 68,46 | 92,71 |
| 328,79 | 107,69 |

PLR in patients with metastases was 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
The Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Patients with NSCLC

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 ≤ 2.68 and PLR > 119.50; and good: NLR ≤ 2.68 and PLR ≤ 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 NSCL.

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. NRL 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 no 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.

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 anti-tumor 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, 22-28).

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).

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.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012; 62: 10-29.
2. O’Byrne KJ, Gatzemeier U, Bondarenko I. Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the phase 3 FLEX study. Lancet Oncol. 2011; 12: 795-805.
3. Douillard JY, Shepherd FA, Hirsh V. Molecular predictors of outcome with gefitinib and docetaxel in previous treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol. 2010; 28: 744-52.
4. Aerts JG, Hegmans JP. Tumor-specific cytotoxic T cells are crucial for efficacy of immunomodulatory antibodies in patients with lung cancer. Cancer Res. 2013; 73: 2381-8.
5. Salagianni M, Baxevanis CN, Papamichail M. New insights into the role of NK cells in cancer immunotherapy. Oncoimmunology. 2012; 1: 205-7.
6. Motohashi S, Okamoto Y, Yoshino I. Anti-tumor immune responses induced by iNKT cell-based immunotherapy for lung cancer and head and neck cancer. Clin Immunol. 2011; 140: 167-76.

7. Vermaelen K, Pauwels R. Pulmonary dendritic cells. Am J Respir Crit Care Med. 2005; 172: 530-51.

8. Tartour E, Zitvogel L. Lung cancer: potential targets for immunotherapy. Lancet Respir Med. 2013; 1: 551-63.

9. Kris MG, Natale RB, Herbst RS. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA. 2003; 290: 2149-58.

10. Nakamoto Y, Guidotti LG, Kuhlen CV, Fowler P. Immune pathogenesis of hepatocellular carcinoma. Journal of Experimental Medicine, 1998; 188(2): 341-50.

11. Rogler G. Chronic ulcerative colitis and colorectal cancer. Cancer Letters. 2014; 345(2): 235-41.

12. Shang K, Bai Y-P, Wang C. Crucial involvement of tumor-associated neutrophils in the regulation of chronic colitis-associated carcinogenesis in mice. PLoS ONE. 2012; 7(12), Article ID e51848.

13. Van Egmond M, Bakema JE. Neutrophils as effector cells for antibody-based immunotherapy of cancer. Seminars in Cancer Biology. 2013; 23(3): 190-9.

14. Granot Z, Henke E, Comen EA, King TA. Tumor entrained neutrophils inhibit seeding in the premetastatic lung. Cancer Cell. 2011; 20(3): 300-14.

15. Kowanetz M, Wu X, Lee J, Granulocyte-colony stimulating factor promotes lung metastasis through mobilization of Ly6G+Ly6C+ granulocytes. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107(50): 21248-55.

16. López-Lago MA, Posner S, Thodima VJ, Molina AM. Neutrophil chemokines secreted by tumor cells mount a lung antitumoral response during renal cell carcinoma progression. Oncogene. 2013; 32(14): 1752-60.

17. Sagiv JY, Michaeli J, Assi S. Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. Cell Reports. 2015; 10(4): 562-73.

18. Sionov RV, Fridlender ZG, Granot Z. The multifaceted roles neutrophils play in the tumor microenvironment. Cancer Microenvironment. 2015; 8(3):125-58.

19. Komurcuoglu B, Ulusoy S, Gayaf M. Prognostic value of plasma D-dimer levels in lung carcinoma. Tumori. 2011; 97(6): 743-8.

20. Unsal E, Atalay F, Atikcan S. Prognostic significance of haemostatic parameters in patients with lung cancer. Respir Med. 2004; 98: 93-8.

21. Van Doormaal FF, Raskob GE, Davidson BL. Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. Thromb Haemost. 2009; 101: 762-9.

22. Gonzalez Barcala FJ, Garcia Prim JM. Platelet count: association with prognosis in lung cancer. Med Oncol. 2010; 27: 357-62.

23. Gislason T, Nøu E. Sedimentation rate, leucocytes, platelet count and hemoglobin in bronchial carcinoma: an epidemiological study. Eur J Respir Dis. 1985; 66: 141-6.

24. Engan T, Hannisdal E. Blood analyses as prognostic factors in primary lung cancer. Acta Oncol. 1990; 29: 151-4.

25. Pedersen LM, Milman N. Prognostic significance of thrombocytosis in patients with primary lung cancer. Eur Respir J. 1996; 9: 1826-30.

26. Aoe K, Hiraki A, Ueoka H. Thrombocytosis as a useful prognostic indicator in patients with lung cancer. Respiration. 2004; 71: 170-3.

27. Cox G, Walker RA, Andi A. Prognostic significance of platelet and microvessel counts in operable non-small cell lung cancer. Lung Cancer. 2000; 29: 169-77.

28. Pilatova K, Zdrazielova-Dubska L, Klement G. The role of platelets in tumor growth. Klin Onkol. 2012; 25 Suppl 2: 2550-57.

29. Kemal Y, Yucel I, Ekiz K, Demirag G. Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. Asian Pac J Cancer Prev. 2014; 15(6): 2651-4.

30. Unal D, Ergolu C, Kurtul N, Oguz A. Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis? Asian Pac J Cancer Prev. 2013; 14(9): 5237-42.

31. Cannon NA, Meyer J, Iyengar P, Ahn C. Neutrophil/lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. J Thorac Oncol. 2015 Feb; 10(2): 280-85.

32. Wu G, Yao Y, Bai C, Zeng J, Donghong Shi. Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients. Thorac Cancer. 2015 May; 6(3): 275-87.

33. Hua Z, Liuwei G, Bin Z, Lianmin Z. Prognostic value of platelet to lymphocyte ratio in non-small cell lung cancer: a systematic review and meta-analysis. Sci Rep. 2016; 6: 22618.

34. Xiao-Bin G, Tian T, Xiao-Jing T, Xiao-Jun Z. Prognostic value of inflammation-based prognostic indices in primary operable non-small cell lung cancer. J Thorac Oncol. 2015 May; 6(5): 807-13.

35. Xiao-Bin G, Tian T, Xiao-Jing T, Xiao-Jun Z. Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis. Sci Rep. 2015; 5: 12493.

36. Pinato D. Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer. Br J Cancer. 2014 Apr 15; 110(8): 1930-5.

37. Wu G, Yao Y, Bai C, Zeng J. Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic c factor in advanced non-small cell lung cancer patients. Thorac Cancer. 2015 May; 6 (3): 275-87.