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The Position of Neutrophils-To-Lymphocytes and Lymphocytes-To-Platelets Ratio as Predictive Markers of Progression and Prognosis in Patients with Non-Small Cell Lung Cancer

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Abstract

BACKGROUND: Non-small cell lung cancer (NSCLC) is an insidious metastasis condition of the lungs often presenting no symptoms at the onset. Defining markers for quick determination of prognosis is essential for building up a treatment strategy.

AIM: The aim of this study is to define the role of the Neutrophils-to-Lymphocytes ratio (NLR) and Platelets-to-Lymphocytes ratio (PLR) as biomarkers in patients with NSCLC, according to the stage and prognosis of the disease.

METHODS: We investigated 20 patients with NSCLC. NLR and PLR are calculated and are evaluated according to the presence or absence of metastasis, stage of the disease, histological type and survival rate.

RESULTS: We found that thirteen of the patients had low NLR, while the rest 7 had high NLR (mean 3.15). By analysing PLR we found that 11 patients have low and 9 have high level of PLR (mean 1.42). After the correlations have been made we discovered that in 90.1% of the patients with low PLR no lymph metastasises were detected, while in 50% of the patients with high PLR lymph metastasises were observed ($\chi 2 = 3.99$; $P = 0.046$). We also discovered that in 84.6% of the patients with low NLR lymph metastases were absent, while in 42.9% with high NLR lymph metastasises were present ($\chi 2 = 1.83$; $P = 0.176$).

CONCLUSION: In conclusion, NLR and PLR were discovered as prominent biomarkers which provide relatively fast determination for prognosis in patients with NSCLC.

Introduction

Lung cancer (LC) is one of the leading causes of cancer related mortality [1]. Non-small cell lung cancer (NSCLC) accounts almost 85% of all LCs, while small cell lung cancer (SCLC) accounts nearly 13% [1]. There are many prognostic factors that are associated with development and progression of LC: TNM status, age, stage, performance, gender, histological variant, serum levels of lactate dehydrogenase LDH, carcinoembryonic antigen CEA and others [2] [3] [4] [5]. Some newer biomarkers like epidermal growth factor receptor EGFR mutations and anaplastic lymphoma kinase ALK rearrangements provide useful information for determining the prognosis and building up a treatment strategy. Unfortunately, these tests are expensive, they can only be evaluated in a small subset of patients and the results take time [6] [7].

The validation of new biomarkers could ease the stratification of high risk patients and could also help make more accurate treatment plan. The relation between the immune response of the patients and the progression and prognosis of the neoplasms is confirmed by multiple analyses [8] [9]. It is known that the tumor microenvironment, which is conditioned by the immune response of the patient and also by the cancer itself, plays a crucial role in the processes of angiogenesis, metastasis and proliferation of the cancer cells [10]. Very important role of the development of these processes is given to the cells

of the extracellular matrix, the cells of the connective tissue and especially to cells such as: lymphocytes, neutrophils, macrophages, dendritic cells, platelets and others.

Lymphocytes are the main cells of the antitumor immune response. Their antitumor capabilities are carried out by cytotoxic T-lymphocytes [11]. The tumor cells are vanished by cytolytic reactions or by induction of apoptosis via membrane receptor of the programmed death. To be effective, the antitumor response requires antigen presentation from the tumor cells or from the antigen presenting cells like macrophages and dendritic cells [12]. Antitumor capabilities of the lymphocytes are ineffective in clinically detectable cancer and are inversely proportional to the tumor size [13]. The cells of the NSCLC escape these immune mechanisms by expression of unstable or bad presented antigens as result of genetic or epigenetic mutations in course of oncogenesis [14].

Neutrophils play main role in the processes of inflammation or antibacterial defense. Chronic inflammation is an established factor that increases the risk of cancer development. Examples are hepatitis B and the inflammatory bowel diseases, which could lead to development of hepatocellular and colorectal carcinoma respectively [15] [16]. The neutrophils take place in the processes of angiogenesis by secretion of pro-angiogenic factors. They directly affect the tumor progression by proteolytic release of epidermal growth factor, transforming growth factor beta and platelet derived growth factor [17]. Furthermore, neutrophils have the capability to influence other tumor promoting cells as T-lymphocytes and NK-cells [18]. Neutrophils have also direct or antibody dependent cytotoxic effect on the cancer cells [17]. It is known that there is neutrophilic polarization, which is caused by different cytokines (TGF-beta, INFs). Polarization defines the development of subpopulations of neutrophils that have antitumor properties as well as subpopulations that support the tumor progression [19]. A high number of neutrophils favor the prognosis according to a number of studies and exactly the opposite effect according to others [20].

Thrombocytes have central place in the processes of growth, progression and metastasis of neoplasms [21]. A hyper coagulation is related to more aggressive cancer disease and even more to thromboembolism, which in turn is one of the leading causes of death in patients with cancer [22] [23]. Platelets release many factors as PDGF, thrombospondin and thrombocytic factor 4 (which favor the hematogenic cancer spread), the adhesion of the tumor cells, invasion, the angiogenesis and in that way the tumor progresses. The prognostic significance of the platelets count in subsets of patients with NSCLC is known for a long time but it has unknown correlation [24] [25] [26] [27] [28].

Many inflammatory indicators attract attention because of their accessibility and prognostic efficacy when determining the prognosis in cancer patients. Such indicators are Neutrophil-to-Lymphocyte ratio (NLR) and Platelets-to-Lymphocyte ratio (PLR). The NLR is an important marker of systemic inflammation. Neutrophils, T- and B-lymphocytes have central role in the antitumor immune response [29]. The disturbance of the normal NLR is considered to be a consequence of the tumor related hypoxia and/or necrosis and is associated with anti- apoptosis effect [30]. The NLR is proven as a prognostic biomarker for determination of the prognosis of patients with different kind of cancer, including colorectal, breast cancer, gastric cancer, pancreatic cancer and esophageal cancer [31] [32] [33] [34] [35]. Many studies try to define the exact place of NLR as a prognostic biomarker in patients with NSCLC. The known evidences show unstable and discrepant results [36]. The prognostic value of the PLR is also associated with some kinds of cancer including gastric, breast, colorectal cancer and NSCLC [37] [38] [39] [40]. The prognostic value of PLR for determining the prognosis of patients with NSCLC is contrary [40] [41]. According to some authors, the high PLR has a negative prognostic value, while others do not succeed to establish clear correlation between prognosis and PLR [42] [43].

The objective of this study is to define the role of the NLR and PLR as biomarkers in patients with NSCLC, according to the stage and prognosis of the disease.

Materials and Methods

This is a retrospective analysis of NLR and PLR in patients with NSCLC at the time of diagnosis and before treatment. Twenty (20) patients with NSCLC were sampled between 2007 and 2016. Their respective NLR and PLR were calculated and evaluated accordingly with emphasis on the presence or absence of metastasis, stage of the disease, histological variants and survival.

NLR and PLR are calculated and are evaluated according to the presence or absence of metastasis, stage of the disease, histological variant and survival.

The study participants comprise of 19 men and 1 woman aged 24 to 75 years (mean 60.7 ± 11.9 years). The patients were initially operated in the thoracic surgery clinic in Stara Zagora between 2007 and 2016. Fifteen percent (15.0%) of the patients were diagnosed in stage T1 and T2; 75% in T3 and T4; lymphatic metastasises were detected in 5 patients; distant metastasises were found in 4 patients (20%). Lung adenocarcinoma was diagnosed in 7 patients, the other 13 patients were diagnosed with

squamous cell lung cancer.

The Statistical Package for the Social Sciences SPSS 16.0 program for Windows was used for statistical analysis. The descriptive statistical tests, including the mean, standard deviation, and median, were calculated according to the standard methods. The frequency of distribution of NLR and PLR and the clinico-pathological parameters in 2x2 contingency tables was analyzed by χ2-test. For all statistical analysis, $p < 0.05$ was considered to be statistically significant.

The study was approved by the local Ethical Committee.

Results

Thirteen of the patients had low NLR, while the rest 7 had high NLR (mean 3.15). By analyzing PLR we found that 11 patients have low and 9 have high level of PLR (mean 1.42). After the correlation has been made we found that in 90.1% of the patients with low PLR no lymph metastases were detected, while in 50% of the patients with high PLR lymph metastasizes were observed (χ2 = 3.99; P = 0.046). In 84.6% of the patients with low NLR lymph metastasizes were absent, while in 42.9% with high NLR lymph metastasizes were present (χ2 = 1.83; P = 0.176) (Table 1).

Table 1: Correlations between NLR, PLR and clinico-morphological factors

Parameter		NLR			PLR		
		Low	High	p	Low	High	p
Age	> 60.7	5	5	0.515	6	4	0.463
	< 60.7	7	3		5	5	
Sex	M	12	7	0.452	10	9	0.381
	F	1	0		1		
Tumor (T)	T1-2	2	1	0.948	2	2	0.737
	T3-4	11	6		9	7	
Nodulus (N)	N0	11	4	0.176	10	4	0.046
	N1-3	2	3		2	4	
Metastsasis (M)	M0	11	5	0.482	10	5	0.134
	M1	2	2		1	3	
Histology type	Adenocarcinoma	4	3	0.589	4	3	0.599
	Squamous cell carcinoma	9	4		7	6	

Discussion

The definition of prognosis is crucial for determination of the treatment strategy in patients with neoplasy. Many studies have tried to discover biomarkers, which could be used for defining the prognosis of patients with NSCLC [44]. The role of development and progression of cancers is the subject of research by many authors. The ratios NLR and PLR are very intensively investigated biomarkers. because of their accessibility and easy interpretation. The important place that NLR and PLR takes in the processes of cancerogenesis is evaluated by comparison of NLR and PLR in healthy persons compared to lung cancer patients. In one of the studies. significantly higher NLR and PLR are found in patients with LC (NLR: 4.42 vs 2.45. PLR: 245.1 vs 148.2) [45].

Our data gained from the small group of patients show that higher NLR and PLR correlate with advanced disease and respectively worse prognosis. Similar results were observed in other studies involving more patients [41] [45] [46] [47] [48] [49].

Increased NLR and PLR calculated from peripheral blood samples are proved as independent predictive marker which is associated with worse prognosis in patients suffering from different kind of cancer including NSCLC [45]. Close to our results were seen in studies which evaluate cancers at different stages. These studies demonstrate that higher NLR and PLR are associated with worse outcome and advanced disease. Increased NLR and PLR determined at the time of diagnosis in non-treated patients are associated with significantly worse survival in a study that includes 94 patients with NSCLC [50].

Even more interesting is the fact that the lower NLR and PLR are associated with better prognosis in patients with NSCLC. Our results show lower NLR and PLR in patients with no lymph metastasis and lack or in smaller degree distant metastasis. A similar conclusion was reported in earlier studies which investigated the combination of both NLR and PLR as prognostic biomarkers as one study that includes 366 patients with NSCLC in advanced stages. The patients were divided in three groups: worse prognosis NLR > 2.68 in the middle NLR < 2.68, PLR > 119.5 and better prognosis NLR < 2.68, PLR < 119.5 [43].

It is observed that the NLR and PLR could change in course of therapy which supposes their estimation in each stage of treatment. In a study that evaluates the change of the values of NLR and PLR show that permanent elevated ratios are associated with worse prognosis and worse survival after treatment [51] [52] [53]. Despite. these observations the place of NLR and PLR is not fully defined. Some authors have not managed to find association of the prognosis and the value of NLR in patients with NSCLC [42]. Some data demonstrated lacks correlation between prognosis and the value of PLR in patients with NSCLC [43].

In conclusion, it can be noted that NLR and PLR are very accessible biomarkers and could be

very useful for relatively fast determination of the prognosis in patients with NSCLC. According to our data, only PLR can be used for prognosis determination, although very small subset of patients was investigated. Usually, higher NLR and PLR are associated with worse prognosis. Unfortunately, the reliability of these biomarkers is not well defined. More investigations are needed to clarify the place of these ratios as biomarkers.

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