Significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in lung cancer

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Abstract

Background: An underlying inflammatory state is an important contributor to carcinogenesis and progression of tumors. Many of the etiological factors in development of lung cancer are linked to persistent inflammation. Neutrophil lymphocyte ratio (NLR) and Platelet lymphocyte ratio (PLR) are markers of systemic inflammatory response that have shown clinical significance in cancer, according to recent research. **Objective:** To evaluate NLR and PLR in lung cancer and compare these parameters in healthy controls. **Materials and Methods:** Clinicopathological details and hematological parameters of complete blood counts were recorded for 106 patients of lung cancer and 106 healthy controls retrospectively. NLR and PLR values were evaluated and compared in the two groups. **Results:** NLR and PLR were significantly elevated in lung cancer patients (NLR 4.44±2.98; PLR 162.72±96.15) as compared to control group (NLR 1.90±0.67, PLR 115.15±29.15) with p value <0.05. NLR showed a sensitivity of 74.5% and specificity 85.8% at optimal cut off value (2.5), as per Receiver operating characteristics (ROC) curve analysis. ROC curve analysis for PLR showed sensitivity 48.1% and specificity 87.8% at optimal cut off value (148.7). **Conclusion:** NLR and PLR are significantly raised in lung cancer. This reflects an underlying inflammatory state that may contribute to development and progression of neoplastic disease in lung. NLR a more sensitive than PLR and may provide useful diagnostic and prognostic information in a country like India that bears a high load of lung cancer cases.

Key words: Neutrophils, Platelets, Lung cancer, Inflammation.

Introduction

Lung cancer has the maximum incidence among all malignancies worldwide. It is the most common cause of cancer related death among males and ranks only second to breast cancer as a cause of cancer related mortality in females [1]. In India lung cancer accounts for the 4th most frequently encountered malignancy [2].

Inflammation is one of the important factors involved in tumor progression in many of the human malignancies. Inflammation leads to tissue injury followed by regeneration and proliferation, a response similar to wound healing. Presence of inflammatory cells and chemical mediators that protentiate cell proliferation and DNA damage at the site of inflammation, results in persistent proliferation of cells thereby contributing to tumor formation. [3] Neutrophils are the primary line of defense against infections. They release various chemical mediators that contribute to inflammation and tissue damage Normally they are short lived cells. However, neutrophils may persist in circulation and at site of inflammation due to delayed apoptosis, thereby contributing to process of resolution at one hand and local tissue damage at another. [4]. Persistent inflammation may set the ground for neoplastic initiation and/or progression. Cigarrete smoking, tobacco, occupational exposure to dust and metals, and chronic obstructive pulmonary disease can lead to abnormal systemic and local inflammatory response that has a critical role in development of lung cancer [5].

Platelets have been traditionally known as major contributor in hemostasis. However, recent research has revealed that platelets also perform proinflammatory and immunomodulatory functions including endothelial activation and leukocyte recruitment that may have a role in neoplastic process. In addition, they can contribute to tumor formation and progression by supporting cellular proliferation, inhibiting apoptosis and promoting

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angiogenesis. Hence, there may be an overlap between inflammatory and cancer promoting functions of platelets [6,7]. Recently, there has been a growing interest in studying inflammatory biomarkers that can be utilized to assess ongoing inflammation in the body.

Neutrophil Lymphocyte ratio [NLR] and Platelet Lymphocyte ratio [PLR] are markers of systemic inflammatory response that have been shown to be of prognostic significance in malignancy including colon cancer, gastric cancer, oral cancer and breast cancer [8-11].

The role of NLR, PLR and other hematological parameters in lung cancer is under research. Large disease burden in India along with high mortality and morbidity associated with lung cancer prompted us to investigate systemic inflammatory markers in these patients.

In the present study, the hematological parameters were studied including NLR and PLR in patients diagnosed as lung cancer as compared to healthy controls in a tertiary care hospital in Western India.

Materials and Methods

Type of study – Retrospective analysis.

Study setting – Department of Pathology in Geetanjali Medical college, Udaipur, Rajasthan, India.

Study design and duration – The present study retrospectively analysed the hematological parameters of 106 patients diagnosed as lung cancer from January 2017 to June 2019. Hematologic parameters of 106 healthy individuals who came for preventive checkup were recorded for control group. The demographic details, pretreatment complete blood count parameters and clinicoradiological findings of the patients were retrieved from clinical records and electronic medical records.

Sampling methods - Blood samples were collected in EDTA vials, and analysed using automated hematological analyser ABX Pentra XL 80 (Horiba medical) and PENTRA XLR (Horiba medical).

Inclusion criteria - The patients diagnosed as lung carcinoma on biopsy were included in the study.

Exclusion criteria - Patients with coexisting heart disease, hematologic disease, carcinoma of other sites and splenectomy were excluded from the study.

Data analysis - Complete blood count evaluation was done and Neutrophil lymphocyte ratio (NLR) and Platelet lymphocyte ratio (PLR) were compared in patients group vs control group. NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count and PLR was calculated as absolute platelet count divided by absolute lymphocyte count.

Ethical approval - Ethical clearance for the study was obtained from Institution Ethics Committee.

Statistical analysis - Data was recorded and analysed using MedCalc software version 19.1 (MedCalc software by Ostend Belgium) All the parameters were recorded and mean value, standard deviation was calculated.

Comparison was done between NLR and PLR in healthy controls and lung cancer patients using Student's t-test. A p-Value of <0.05 was considered significant. Receiver operating characteristics curve were plotted and optimal cut-off value determined for NLR and PLR in lung cancer patients vs healthy controls.

Results

A total of 106 cases of lung cancer and 106 healthy controls were included in the study. Mean age for lung cancer patients was 61.6±10.4 years. 82 (87.7%) were males and 13 (12.3%) patients were females. Histological types were recorded as 99 (93.4%) cases of non small cell lung cancer and 7 (6.6%) cases of small cell lung carcinoma. The value of NLR (Cases- 4.44±2.98; Controls- 1.90±0.67) was found to be statistically significant i.e. $p<0.05$ and PLR (Cases- 162.72±96.15; Controls- 115.15±29.15) among the cases and controls was also found to be significant i.e. $p<0.05$ (Table 1).

Table-1: NLR and PLR in lung cancer and controls.

	N	NLR	Range	PLR	Range
Lung cancer	106	4.44	1.01-16.83	162.72	23.04-475.91
Controls	106	1.90	1.10 - 3.70	115.15	61.71-216.49

ROC curve analysis (Figure 1(a)) yielded sensitivity of NLR as 74.5 and specificity as 85.8, with optimal cut off value of 2.5 and area under curve 0.847 (95% confidence interval: 0.791 to 0.893). PLR (Figure 1(b)) showed a specificity of 87.8 and a sensitivity of 48.1, with area under curve 0.632, and an optimal cutoff value at 148.7 (95% confidence interval: 0.564 to 0.697).

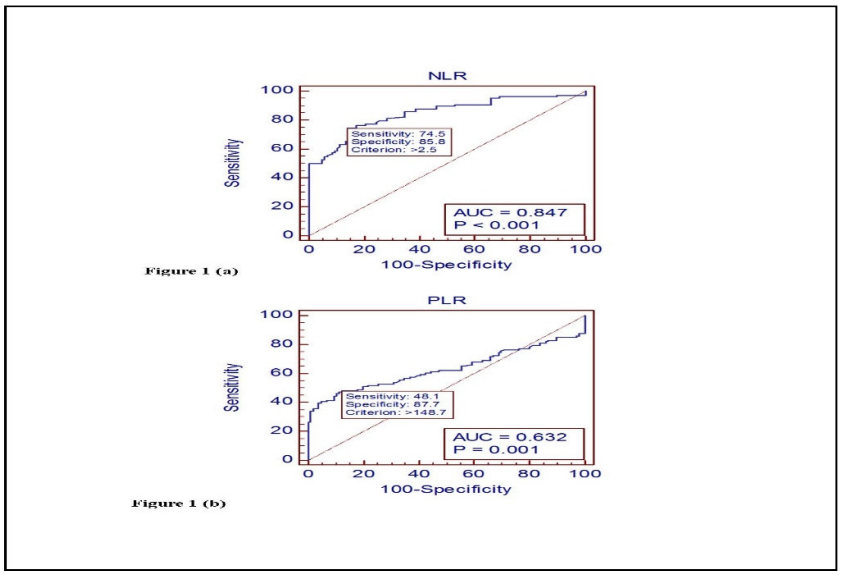

Figure-1: Receiver operating characteristics (ROC) curve for (a) Neutrophil lymphocyte ratio (NLR) and (b) Platelet lymphocyte ratio (PLR).

Discussion

Lung cancer ranks 4th in incidence among malignancies in India, with 67,795 new cases detected in 2018 as per GLOBOCAN data [2]. It is the leading cause of cancer related deaths worldwide [1] and 3rd most common cause of cancer deaths in India [2]. The most important causative risk factor for lung cancer is smoking, followed by other environmental and occupational determinants such as exposure to passive smoking, industrial chemicals, asbestos, arsenic, beryllium, pollution in indoor and outdoor environment, agricultural pesticides and ionizing radiation [12].

In the present study, NLR and PLR were studied, that are markers of systemic inflammation, in patients of lung cancer. Both NLR and PLR were found to be elevated significantly in lung cancer patients as compared to healthy controls. NLR and PLR also have diagnostic significance in patients of lung cancer. ROC analysis revealed that NLR has a better sensitivity (74.1) than PLR for diagnosis of lung cancer, with area under curve 0.847 at an optimal NLR cut off value of 2.5. Therefore, NLR is better for the diagnosis of lung cancer, and may be a useful pointer to evaluate the patient for a possible underlying lung malignancy in appropriate clinical setting.

These results are comparable to other studies that have shown that markers of systemic inflammatory state including NLR and PLR are raised in lung cancer [13].

Elevated NLR may be associated with reduced survival in lung cancer [14,15]. This indicates an underlying inflammatory process that may contribute in initiation and progression of the disease.

Neutrophils are important component of immune system and constitute the body's first line of defence against microbial infections. They produce a variety of active mediators including reactive oxygen species which play a key role in inflammatory process that may eventually lead to tissue damage. Recent research indicates that the neutrophils may have additional roles in resolution of inflammation and adaptive immune response [4]. In addition, activation of neutrophils may also contribute towards the development of autoimmune and chronic inflammatory disorders [16].

Chronic inflammation is an important factor in the development and progression of many of the human cancers. Inflammatory pathways not only lead to activation of transcription factors and tumorigenic factors, they also inhibit the antitumor immune response [17].

Inflammation occurring due to infections, extrinsic agents such as tobacco smoke, asbestos, or inflammatory mediators produced by neoplastic cells can lead to activation of transcription factors such as NF-κβ and HIF-1 that can further potentiate inflammation by chemical mediators, and recruit inflammatory cells including neutrophils and other inflammatory cells. This results in an autoamplification loop which contributes to tumor progression [17,18].

IL-1, which is produced by tumor cells themselves or by cells of tumor microenvironment, also plays an important role in inflammation related tumorigenesis, by stimulating other cells to secrete chemical mediators that promote angiogenesis and tumor progression [19].

Chronic activation of immune system associated with inflammation contributes in development of a neoplastic clone in many of the cancers. Secretion of cytokines in inflammation may promote angiogenic and antiapoptotic phenotype, thereby facilitating the tumor cells to escape cell mediated immunity [5,17]. Smoking is the major culprit in development of lung cancer [5,20]. Tobacco and other toxic particles in inhaled smoke cause inflammation in lung airways and parenchyma, which promotes recruitment of inflammatory cells.

Passive smoking also can lead to a similar injury in the lungs. Occupational dusts such as asbestos, nickel, arsenic and silica are known to cause interstitial lung disease, and there may be an increased risk of lung cancer associated with long standing exposure [5].

Chronic obstructive pulmonary disease (COPD) is associated with persistent inflammation, repeated tissue injury and repair. COPD leads to abnormal inflammatory response, which is local and systemic, and also increased predisposition to lung cancer [5,21]. Predisposition to lung cancer in idiopathic pulmonary fibrosis may occur due to oxidative DNA damage and repair leading to mutations in tumor suppressor genes [22].

Chronic pulmonary infections such as tuberculosis and Chlamydia pneumonia may also be a factor in lung cancer development [5,20].

Thus, persistent inflammation causes repetitive tissue injury, repair, proliferation and angiogenesis, with contribution by inflammatory cells, cytokines, interleukins and other chemical mediators. This may eventually progress to uncontrolled cell proliferation as the tumour suppressor mechanisms are overcome and culminate in development of a neoplasm.

Neutrophils have been known as the key players in immunity and primary defence against pathogens. However, with recent research, these cells are being implicated to have a potential role in tumor initiation, proliferation, angiogenesis and metastatic spread [3,8,23]. Elaboration of chemical mediators including proteases and reactive oxygen species by neutrophils may promote the initiation of tumor. Neutrophils also suppress the antitumor mechanisms of the body, thus facilitating tumor progression.

They produce growth factors and metalloproteinases which lead to angiogenesis [23]. Adhesion molecules expressed on neutrophils may be involved in metastases. Emboli of tumor cells attached to platelets and neutrophils may metastasize [3]. Also, neutrophils may contribute to the metastatic process by suppressing Natural Killer cells. Multiple subsets of neutrophil population have been identified, that may perform varied functions. Some of these subpopulations have a protective role such as inhibiting metastases. Exploring the role of neutrophils in cancer can lead to useful information, which may permit the development of newer therapeutic strategies [23].

In the present study, PLR was elevated in lung cancer patients. PLR has been shown to have prognostic significance in lung cancer [15]. PLR may also help in predicting response to chemotherapy in non small cell lung cancer [24].

Platelets have a major role in hemostasis. In addition, they play an important role in inflammation by releasing proinflammatory mediators and promoting leukocyte recruitment and migration to site of inflammation [6]. Immune modulatory functions of platelets may have a significant role in tumorigenesis by affecting endothelium and leukocytes [7].

Platelets have been shown to induce proliferation of colon and pancreatic cancer cells [25]. They secrete growth factors that promote tumor angiogenesis [26]. In addition, platelets may inhibit Natural Killer (NK) cell mediated lysis of tumor cells in the bloodstream, thereby facilitating metastatic spread [27].

Thus, platelets may play an important role in tumor progression and spread, and this may form the basis for future anti-cancer therapeutic agents.

Neutrophil Lymphocyte Ratio (NLR) and Platelet lymphocyte ratio (PLR) are markers of systemic inflammation. NLR has been correlated with clinical stage, overall and cancer specific survival in colorectal cancer [8]. NLR and PLR have prognostic significance in gastric cancer [9]. NLR/PLR profile estimation has been shown to predict remission in breast cancer [11]. In oral cancer, these parameters have been used in developing a prognostic scoring system [10].

Many of the predisposing factors of lung cancer have their basis in persistent inflammatory state. Therefore, it is understandable that inflammatory markers such as NLR and PLR are raised in lung cancer. NLR and PLR may be used as predictors of lung cancer.

These parameters are easily available at a low cost, on a complete blood count. In developing countries, they may be especially useful to probe the clinician to investigate a patient further. The present results are comparable with other studies. However, further research with a larger sample size and inclusion of prognostic data may provide more information.

Conclusion

NLR and PLR are hematological markers of systemic inflammation that are significantly raised in lung cancer.

This reflects an ongoing inflammatory state in the body that may contribute to development and progression of the disease. With availability of automated hematological analysers in most health care centres, these parameters can be easily assessed at a low cost to provide useful diagnostic and prognostic information in a country like India that bears a high load of lung cancer cases.

What this study adds the existing knowledge?

As there is a paucity of literature on the current topic from India, this study contributes significantly by investigating the inflammatory biomarkers NLR and PLR in lung cancer patients. It provides useful insight by relating lung cancer with systemic inflammation and newer diagnostic and treatment strategies may be the next frontiers of research based on this knowledge.

Author's contribution

Dr. Ashumi Gupta: Study design and concept, data analysis and processing, literature compilation, drafting the manuscript.

Dr. Urvashi: Data collection and processing, materials, literature review.

Dr. Mohanlal Gupta and Dr. Narendra Mogra: Guidance, study concept and design, supervision.

Dr. Medha Mathur: Data processing and analysis, review.

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