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# Prognostic Value of Platelet to Lymphocyte Ratio in Patients with Non-Small Cell Lung Cancer

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## ABSTRACT

**Background:** The prognostic value of Platelet-to-lymphocyte ratio (PLR) in patients with non-small-cell lung cancer (NSCLC) is still indistinct. We conducted this study to assess the prognostic significance of pretreatment PLR in patients with unresectable NSCLC.

**Aim of the Work:** to assess the prognostic significance of pre-treatment PLR in patients with NSCLC.

**Material and Methods:** we retrospectively reviewed 130 patients treated for NSCLC with definitive/palliative chemotherapy and/or radiotherapy in Ain-Shams University hospital, Clinical Oncology department between January 2014 and December 2016. Pre-treatment CBC was available for the 130 patients to calculate PLR by dividing the absolute platelet count by the absolute lymphocytic count.

**Results:** Out of 130 patients with available pre-treatment complete blood picture, population age ranged from 23 to 87 years. Male to female ratio was 4.8:1. Adenocarcinoma presents 51% of cases. Unresectable stage II and stage III present 2% and 27% respectively, while Stage IV presents 69%. Using a cut-off value of 150, high PLR>150 was significantly associated with poor overall survival (OS) (median OS: 10.33 months; 95% CI: 6.23-14.42), compared to patients with PLR<150; (median OS: 24.63 months, 95% CI: 11.5-37.76, p=0.008), but not PFS. In multivariate analysis, PLR>150 was an independent poor prognostic factor for OS; (HR=1.9, 95% CI; 1.092-3.3, p=0.023).

**Conclusion:** High PLR is associated with poor OS in patients with unresectable NSCLC.

**Keywords:** Platelet to Lymphocyte ratio, Non-small cell lung cancer, prognostic factor.

## INTRODUCTION

Lung cancer remains the most common cancer in the world, both in term of new cases (1.8million cases, 12.9% of total) and deaths (1.6 million deaths, 19.4% of total cancer cases). Although lung cancer is the most common cancer worldwide among men, it ranks second in more developed regions (490,000 cases) after prostate cancer (759,000 cases) in 2012 worldwide statistics [(1)]. In Egypt, lung cancer comes forth in ranking with crude incidence rate 8.2% of all cases among males. The age standardized rate and crude incidence rate for lung cancer per 100,000 were 10.1 and 7.6 in lower Egypt, 10.8 and 6.3 in middle Egypt, 6.7 and 6 in upper Egypt Respectively[(2)]**.** To date, disease stage based on tumor-node-metastases (TNM) classification is the best prognostic factor [(3)]**.** In an attempt to better estimate the prognosis, many prognostic parameters have been investigated, such as performance status, weight loss, biomarkers and other factors. EGFR mutations may be a positive prognostic factor for survival in advanced NSCLC patients treated with chemotherapy with or without erlotinib, and may predict greater likelihood of response. Patients with KRAS-mutant NSCLC showed poorer clinical outcomes when treated with erlotinib and chemotherapy [(4)]**.** Recently, it is widely recognized that systemic inflammatory response plays an important role in the initiation and progression of cancer. Molecular factors and biological pathways including upregulation of cytokines, chemokines and inflammatory mediators, promotion of angiogenesis, local immunosuppression, inhibition of apoptosis, and DNA damage are involved in this response and are associated with an increased risk of metastasis. There is increasing evidence that measures of the systemic inflammatory response, such as neutrophil, lymphocyte, C-reactive protein (CRP), and the Glasgow Prognostic Score (GPS), have prognostic value in a variety of cancers [(5)]**.** The platelet– lymphocyte ratio (PLR), defined as the absolute platelet count divided by the absolute lymphocyte count, has gained a lot of interest in recent years. Published data suggested that elevated PLR was an important prognostic factor in esophageal cancer, gastric cancer, renal cell cancer, and malignant pleural mesothelioma [(6)]**.** In a prospective study done by **Sanchez-Lara and colleagues** [(7)] in Mexico from 2009 to 2011, on 119 patients with stage III-IV NSCLC, treated with chemotherapy, evaluating prognostic significance of baseline PLR on overall survival, using cut-off value: 150. Results were statistically significant with HR:1.16, 95%CI: (0.52-2.50). Another study done by **Liu et al** [(8)] in China, retrospectively reviewed data of 210 patients with stage III-IV NSCLC treated with chemotherapy from 2001 to 2012, also evaluating prognostic significance of baseline PLR on overall survival, using cut-off value:150. HR was 2.025, 95% CI:(1.4-2.9). However, the prognostic value of PLR in NSCLC remains uncertain. Therefore, in this study, we



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aimed at investigating the prognostic significance of PLR in NSCLC patients.

## PATIENTS AND METHODS

**Study design and Data selection:** The study involved 130 patients with histologically confirmed Non-small cell lung cancer of any stage, aged 18 years or above, treated between January 2014 and December 2016, in thoracic oncology and chemotherapy units, department of clinical oncology and nuclear medicine, Ain Shams University hospitals, Cairo, Egypt. Patients were retrospectively reviewed for the prognostic impact of baseline Platelet to Lymphocyte Ratio (PLR). All available data (including patient, tumor, and treatment characteristics), were extracted from patients' files, all available prognostic data were documented as well as baseline lymphocyte, and platelet counts. We excluded patients with synchronous malignancies, histologic types of lung cancer other than non small cell variants or pre-treatment infection or hematologic diseases that may affect blood cell counts. **The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from each participant in the study.** ***Data Analysis:*** Statistical Analysis Software (IBM SPSS, version 20) was used for data analysis. First, descriptive analysis for the whole study population was done using count and percentage for categorical variable and mean $\pm$SD for quantitative variables. Univariate frequency analysis was performed using Chi-square test and Fisher exact test for categorical variables and independent-t test and paired-t test for numerical variables. Statistical significance was established at a p-value of less than 0.05.

## RESULTS

**Patient demographics:** In the period between Jan 2014 - Dec 2016, five thousand two hundred sixty five new cases were registered in our centre; a total of 354 confirmed non small cell lung cancer cases presented to our thoracic malignancies unit. Lung cancer represented 6.73% of all newly diagnosed cases.

**Table (1):** Demographic data

| Demographic data | No. | % |
|---|---|---|
| **Age (years)** | | |
| **<60 years** | 69 | 53.33 |
| **≥60 years** | 61 | 46.67 |
| **Sex** | | |
| **Male** | 107 | 82.3 |
| **Female** | 23 | 17.7 |
| **Performance status** | | |
| **0** | 2 | 1.5 |
| **1** | 68 | 52.4 |
| **2** | 45 | 34.5 |
| **3** | 9 | 6.9 |
| **4** | 6 | 4.6 |
| **Residence** | | |
| **Urban** | 121 | 93.1 |
| **Rural** | 9 | 6.9 |
| **Smoking** | | |
| **Smoker (current or former)** | 99 | 76.1 |
| **Never smoker / not reported** | 31 | 23.9 |
| **Medical history(Co-morbidities)** | | |
| **Chronic obstructive pulmonary disease** | 82 | 63 |
| **Diabetes mellitus** | 23 | 17.7 |
| **Hypertension** | 21 | 16.1 |
| **Cardiac disease** | 9 | 6.9 |
| **Bronchial asthma** | 12 | 9.2 |
| **Interstitial lung disease** | 4 | 3.1 |
| **Pulmonary tuberculosis** | 2 | 1.5 |

**Clinico-pathologic and prognostic data:**

The most common symptom at presentation was dyspnea (30%) followed by clinically relevant weight loss (28%) (defined by unintentional unexplained loss of 5% of body weight for the last month or 10% of body weight for the last 6 months), chronic cough (24%), chest pain (15%), haemoptysis (14%), hoarseness of voice (9%), neurological symptoms as increased intra cranial tension symptoms or focal neurological deficit (5%), and bone pain (0.7%). The median duration of presenting symptom was 2 months. Regarding the histological type, 51% of patients were diagnosed with pulmonary adenocarcinoma, 27% of patients with squamous cell carcinoma and 22% of patients with NSCLC not otherwise specified (NOS). TNM staging system according to the American Joint Cancer Committee (AJCC)7$^{th}$ editionwas analysed using clinical and radiological data of the study population as shown in the following table:

**Table (2):** Clinical staging

| Tumor | No. | % |
|---|---|---|
| T1 | 3 | 2.3 |
| T2 | 23 | 17.7 |
| T3 | 55 | 42.3 |
| T4 | 49 | 37.7 |
| **L.N** | | |
| N0 | 6 | 4.6 |
| N1 | 16 | 12.3 |
| N2 | 98 | 75.4 |
| N3 | 10 | 7.7 |
| **Metastasis** | | |
| M0 | 41 | 31.6 |
| M1 | 89 | 68.4 |
| **Clinical stage** | | |
| II | 3 | 2.3 |
| III | 38 | 29.3 |
| IV | 89 | 68.4 |
| **Sites of metastasis** | n=89 | % |
| Pleural effusion | 35 | 40 |
| Bone | 17 | 19 |
| Non-regional lymph nodes | 10 | 11 |
| Brain | 9 | 10.2 |
| Contra-lateral lung | 7 | 7.7 |
| Liver | 7 | 7.7 |
| Adrenals | 4 | 4.4 |

Among the 130 patients with available pre-treatment CBC, platelet to lymphocyte ratio (PLR) range was (17-750) with median PLR of 177 and Mean PLR was 201. Progression-free survival is defined as the time from pathological diagnosis to disease progression or death from any cause. Median PFS of the whole population was estimated to be 6.3 months with 95% CI;(5.2-7.3) and a SD=0.5 months, while mean PFS was estimated to be 9.3 months with a 95% CI;(7.7-11) and a SD=0.8 months.

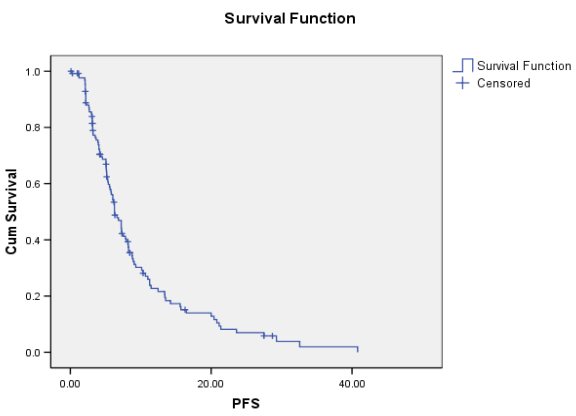


**Figure (1):** Kaplan-Meier curve illustrating progression free survival for the study population.

Univariate analysis of PFS in relation to different clinical parameters of the study population has shown a statistically significant association between PFS and clinical staging, though no significant association between PFS and sex, age, smoking, weight loss, pathological type and pathological grade. Chi-Square test was used as a test of significance for all studied clinical parameters.

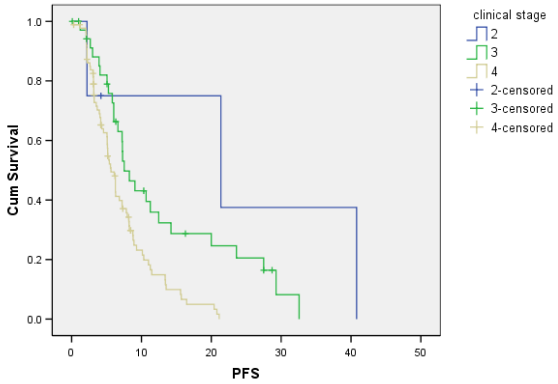


**Figure (2):** Kaplan Meier curve illustrating the statistically significant correlation between PFS and clinical staging.

Overall survival is defined as the time from pathological diagnosis to death from any cause. Median OS of the whole population was estimated to be 11.3 months with 95% CI;(6.8-15.75) and a SD=2.3 months, while mean OS was estimated to be 17.3 months with a 95% CI;(13.9-20.7) and a SD=1.7 months.

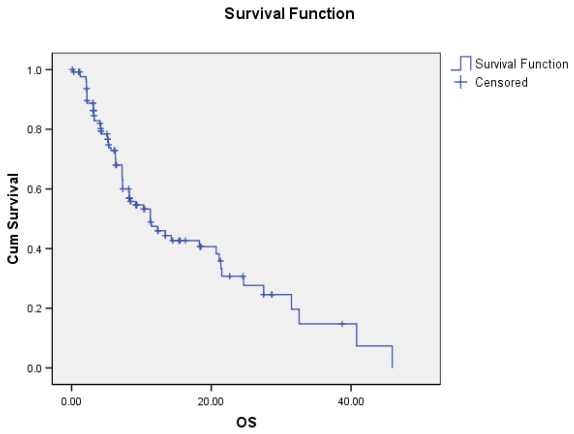

**Figure (3):** Kaplan Meier curve illustrating OS for the study population.

Univariate analysis of OS in relation to different clinical parameters of the study population has shown a statistically significant association between OS and clinical staging, though no significant association between OS and sex, age, smoking, weight loss, pathological type or pathological grade. Chi-Square test was used as a test of significance for all studied clinical parameters.

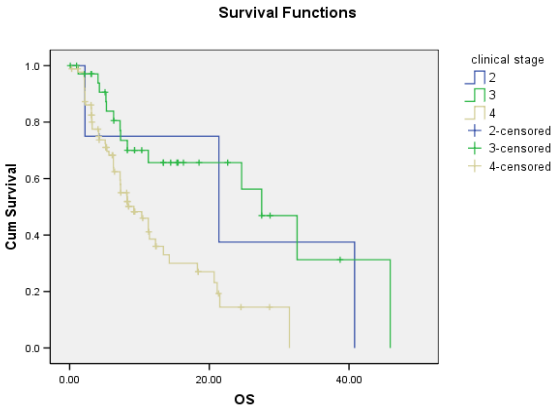


**Figure (4):** Kaplan Meier curve illustrating the statistically significant association between OS and clinical staging.

For group of patients with PLR below 150; median PFS was 7.830 months with 95% confidence interval (6.65-9), and standard deviation 0.6 months, while for patients with PLR above 150; median PFS was only 5.830 months with 95% confidence interval (5-6.65), and standard deviation=0.419 months. (P-value = 0.118) for correlation between PFS and PLR; statistically insignificant for shorter PFS in the elevated PLR group.

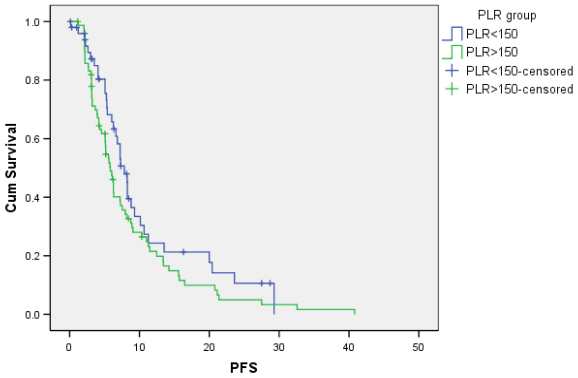


**Figure (5):** Kaplan Meier curves illustrating the relationship between PFS and different PLR groups.

For patients with PLR below 150; estimated OS was 24.6 months with 95%CI (11.5-37.8) and SD of 6.7 months, while for patients with PLR above 150; estimated median OS was 10.33 months with 95%CI (6.2-14.4) and SD of 2 months. Results are positive and statistically significant for shorter overall survival in the elevated PLR group, (p value=0.008).

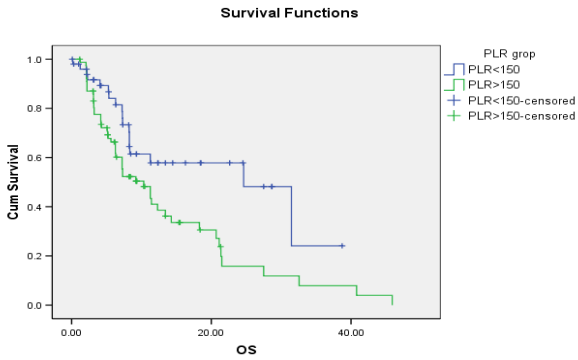


**Figure (6):** Kaplan Meier curves illustrating the relationship between OS and different PLR groups.

Multivariate analysis combining PLR with clinical staging in relation to overall survival has shown that PLR>150 was an independent poor prognostic factor for overall survival (HR=1.9, 95% CI; (1.092-3.3), p value=0.023).

## DISCUSSION

The present study analyzed the prognostic significance of baseline platelet to lymphocyte ratio of 130 pathologically confirmed non small cell lung cancer patients who were diagnosed and treated over a period of 3 years at our center. The present study couldn't establish a statistically significant impact for previously identified prognostic factors on both progression free and overall survival, except for TNM staging. This may be attributed to small sample size in comparison to related studies assessing different prognostic factors in NSCLC patients. Regarding the prognostic significance of baseline Platelet to Lymphocyte Ratio (PLR) in patients with NSCLC, which is our main study point; our study results were statistically insignificant for shorter PFS in the elevated PLR group. Regarding the impact of baseline PLR on overall survival; Results were statistically significant for shorter overall survival in the elevated PLR group. Multivariate analysis

combining PLR with clinical staging (statistically significant parameters) in relation to overall survival has shown that PLR >150 was an independent poor prognostic factor for overall survival. Results of the present study were comparable to results from a study published by **Toda and colleagues** [(9)]; 327 NSCLC patients treated surgically with or without adjuvant chemotherapy at the department of thoracic surgery, Graduate School of Medicine, Osaka City University, Osaka, Japan between (2008-2012). Using a cutoff value 162 for preoperative PLR; the five-year overall survival rates for patients with low and high PLR were 78% and 57% ($P < 0.01$) for all patients, and 69% and 37% ($P < 0.01$) for patients who received adjuvant chemotherapy, respectively. Similarly, the five year disease-free survival rates for patients with low and high PLR were 66% and 62% ($P = 0.03$) for all patients, and 47% and 14% ($P < 0.01$) for patients who received adjuvant chemotherapy, respectively. Cox proportional hazard regression indicated that high PLR was an independent prognostic factor for both overall and disease-free survival in the adjuvant chemotherapy group. Results were also consistent with the study results published by **Lan and colleagues** [(10)]who studied a total of 174 NSCLC patients with non-small cell lung cancer (NSCLC) who underwent radical lung cancer surgery were studied. The results indicated that both high PLR (>148.6) and NLR (neutrophil to lymphocyte ratio >2.9) were related to a high rate of postoperative pulmonary complications significantly (49.3% vs. 29.1%, $P = 0.007$; 50.7% *vs*. 28.6%, $P = 0.003$). Moreover, NSCLC patients with a high PLR level (> 148.6) was significantly associated with a lower one-year OS (90.3% *vs*. 77.5%, $P = 0.034$). Results were also comparable with two large meta-analyses of similar studies with the same end points. The first one analyzed total of seven studies involving 1,554 patients with stage I-IV NSCLC**.** Pooled results demonstrated that high PLR was associated with poor OS (HR: 1.60, 95% CI: 1.34– 1.90) and poor DFS (HR: 1.38, 95% CI: 1.11– 1.73) [(11)]**.** The other meta-analysis utilized data from 12 studies with total of 2,889 patients with stage I-IV NSCLC. The pooled HR for death of 1.492 (95% CI: 1.231– 1.807, $P < 0.001$) indicated that patients with an elevated PLR are expected to have a shorter overall survival (OS) after treatment [(12)]**.** In a study conducted by **Wu and colleagues** [(13)] a total of 366 primary NSCLC patients with stage III or IV were included. NLR (neutrophil lymphocyte ratio) and PLR were calculated and NLR > 2.68 or PLR >119.50 were defined as elevated. PLR appeared to be an independent prognostic factor (overall survival [OS]: hazard ratio [HR] = 1.918, $P = 0.003$; progression-free survival [PFS]: HR = 1.822, $P = 0.007$ in condition of NLR $\leq$ 2.68.

## CONCLUSION

High baseline PLR is associated with poor prognosis in patients with NSCLC. Further studies with larger sample size are required for validation, generalization of results on wider scale population and future utilization of this simple, cheap and available prognostic marker in daily management of NSCLC patients.

## CONFLICTS OF INTEREST

There are no conflicts of interest.

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