

RESEARCH ARTICLE

Elevated Serum Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios Could be Useful in Lung Cancer Diagnosis

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Abstract

Background: Lung cancer (LC) is still the primary cause of cancer deaths worldwide, and late diagnosis is a major obstacle to improving lung cancer outcomes. Recently, elevated preoperative or pretreatment neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) detected in peripheral blood were identified as independent prognostic factors associated with poor survival with various cancers, including colon cancer, esophageal cancer, gastric cancer and breast cancer. **Objective:** The aim of this study was to examine whether MPV, NLR and PLR could be useful inflammatory markers to differentiate lung cancer patients from healthy controls. An investigation was also made of the relationship between these markers and other prognostic factors and histopathological subgroups. **Materials and Methods:** Retrospectively eighty-one lung cancer patients and 81 age-sexes matched healthy subjects included into the study. Patients with hypertension, hematological and renal disease, heart failure, chronic infection, hepatic disorder and other cancer were excluded from the study. The preoperative or pretreatment blood count data was obtained from the recorded computerized database. **Results:** NLR and PLR values were significantly higher in the LC patients 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 statistically significant relationship was determined between these markers (MPV, NLR and PLR) and histopathological subgroups and TNM stages. **Conclusions:** NLR and PLR can be useful biomarkers in LC patients before treatment. Larger prospective studies are required to confirm these findings.

Keywords: Lung cancer - platelets - neutrophils - lymphocytes - ratios

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Introduction

Lung cancer (LC) is still the primary cause of cancer deaths worldwide, and late diagnosis is a major obstacle to improving lung cancer outcomes (Jemal et al., 2011). More than half of patients (56%) with lung cancer at the time of diagnosis have advanced or metastatic disease (Howlander et al., 2009) and even with chemotherapy have a median survival of one year or less (Sandler et al., 2006). Although various factors for prognosis of lung cancer and different predictive factors for response to different agents have been identified in previous studies (Tanner et al., 2012), there is still no promising predictive factor that can be simply detected and closely linked to clinical treatment response and survival for advanced LC patients; (Donnem et al., 2012). Tumor stage and performance status (PS) are the most important factors (Hoang et al., 2005; Groome et al., 2007) that could predict patient prognosis.

Inflammation seems to play a critical role in the development and progression of numerous cancers

by promoting cancer cell proliferation and survival, angiogenesis, tumor metastasis and impacting tumor response to systemic therapies (Mantovani et al., 2008). It has been suggested that neutrophils, as well as T and B lymphocytes and platelets play a prominent role in the tumor inflammation and immunology (Schreiber et al., 2011). Based on this theory several inflammatory markers in blood count (platelets, neutrophils and lymphocytes or neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) have been studied in various malignant tumors. An increase in peripheral neutrophils is thought to reflect an intrinsically aggressive nature of tumor cells because it mainly results from hematopoietic cytokines actively produced by tumor cells (Lee et al., 2012). Neutrophils can promote tumor growth and metastasis by remodeling the extracellular matrix. They release reactive oxygen species (ROS), nitric oxide (NO), and arginase and suppress the T-cell response (De Larco et al., 2004).

On the other hand platelets play an important and

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multifaceted role in cancer progression. They can promote tumor growth with increasing angiogenesis (Howlander et al., 2009) by the cytokine vascular endothelial growth factor (VEGF) (Dvorak et al., 1995). Mean Platelet Volume (MPV), which can be easily evaluated by hematological analyzers, is a convenient marker of platelet functions and activation. It shows the average size of platelets and reflects the platelet production rate and stimulation (Kai et al., 2005). Larger platelets are more metabolically and enzymatically active than smaller platelets (Mangalpally et al., 2010).

Recently, elevated preoperative or pretreatment NLR, PLR and MPV detected in peripheral blood have been identified in various cancers, including colon cancer, esophageal cancer, gastric cancer ovarian cancer and breast cancer (Walsh et al., 2005; Gwak et al., 2007; Smith et al., 2009; Sharaiha et al., 2011; Thavaramara et al., 2011; Azab et al., 2012; Kilincalp et al 2013).

As a marker of inflammation and immunology, NLR, PLR and MPV are highly repeatable, inexpensive and widely available. The aim of this study was to examine whether MPV, NLR and PLR could be useful inflammatory markers to differentiate lung cancer patients from healthy controls. An investigation was also made of the relationship between these markers and other prognostic factors and histopathological subgroups.

Materials and Methods

The study was conducted as a retrospective investigation of lung cancer patients who had been referred to the Medical Oncology Department of 19 Mayıs University Hospital between January 2008 and December 2012. Approval for the study was granted by the 19 Mayıs University Ethics Committee. Patients with hypertension, hematological, hepatic and renal disease, heart failure, chronic infection, autoimmune disease, splenectomy, other cancers or patients using drugs which could affect platelet count and/or function were not included in the study.

All patients included in the study were hospitalized for the primary diagnosis, were therapy naive and were histologically or cytologically diagnosed with primary lung cancer, which was staged according to the tumor–node–metastasis (TNM) criteria (AJCC 7th edition criteria 2010-for SCLC as well as NSCLC). 21 cases of lung cancer were excluded from the study due to lack of data. Data collection included patient demographics, clinicopathological parameters and pretreatment haematological parameters. Control subjects were individually selected from persons attending check-ups at the outpatient clinic. The study groups were designed as early stage (stage I-II-IIIa) lung cancer and advanced stage (stage IIIb-IV) lung cancer.

The pre-operative data was obtained from the recorded computerized database. Routinely in our hospital, CBC are measured by Siemens Healthcare Diagnostic Item ADVIA 2120i and blood samples measured with potassium-ethylendiaminetetraacetic acid are analysed one hour after vein-puncture. The normal MPV value in our laboratory ranges between 7.0 and 11.1 fL. NLR and PLR were obtained from the absolute neutrophil count or platelet

Table 1. Demographic Features of Pre-operative Patients and Controls

	Patients	Controls
No. of patients	81	81
Age, year (mean)	55	54
Gender Female/male	28/53	28/53
Stage Early/advanced	25/56	
Histology Adenocarcinoma	32	
Squamous carcinoma	27	
SCLC ¹	22	

¹small cell lung cancer

Table 2. Comparison of the Inflammatory Parameters

	Patients	Controls	P value
MPV ¹	7.70±0.11	7.85±0.11	0.244
NLR ²	4.42±0.51	2.45±0.31	0.000
PLR ³	245.174±25.63	148.23±6.51	0.002

*Data are presented as means±standard deviation; ¹mean platelet volume; ²platelet to lymphocyte ratio; ³neutrophil to lymphocyte ratio

count, respectively, divided by the absolute lymphocyte count.

Statistical analysis

Statistical analyses were performed with SPSS software (SPSS 15.0, Chicago, USA). All parameters were expressed as means±standard deviation. The normality of distribution was checked initially by the Shapiro Wilk test and parametric or non-parametric tests were applied to data with normal or non-normal distributions. The Mann-Whitney U test was used to compare the parameters of pre-treatment NSCLC cancer patients and control subjects. Correlations between the NLR, PLR and MPV and categorical variables (stage, grade, histopathologic subgroup) were tested with the Mann-Whitney U test. The results were expressed as mean±Standard deviation (SD). A value of $p \leq 0.05$ was considered statistically significant.

Results

According to the inclusion criteria, 81 lung cancer patients and 81 age-sex matched healthy subjects were identified between January 2008 and December 2012. The baseline characteristics are shown in Table 1. The median age was 55 years (range 18-82 years). The majority of the patients were male (65%) and advanced stage (70%) and 40% had adenocarcinoma. There was no statistically significant difference between the groups regarding age and gender.

NLR and PLR values were significantly higher in the lung cancer patients 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) (Table 2). No statistically significant relationship was determined between these markers (MPV, NLR and PLR) and histopathological subgroups and TNM stages.

Discussion

The results of this study indicate that the LC patients had significantly higher NLR and PRL values compared

with the healthy control group. Elevation in MPV values were statistically non-significant. Moreover, no relationship was observed between NLR, NLR values and TNM stages and histopathological subgroups.

The explanation for the association between elevated NLR and PLR values in many tumors is not fully understood. However, we can discuss the probable pathways. Many cancers arise from sites of infection and inflammation. In the development and progression of a cancer, inflammation is a crucial and essential process (Balkwill et al., 2001). Our findings support the predictive values of these inflammatory markers (i.e. NLR and PLR) parallel to the well-established association between cancer and inflammation (Balkwill et al., 2001). These findings also corroborate those of prior studies of other types of cancers (Thavaramara et al., 2011; Kilincalp et al., 2013). We advocate that an understanding of the role of neutrophils, platelets, and lymphocytes in cancer will aid in elucidating the association between cancer and inflammation.

Platelets play an important and multifaceted role in cancer progression. They can promote tumor growth by increasing angiogenesis (Bambace et al., 2011) via the cytokine vascular endothelial growth factor (VEGF) (Dvorak et al., 1995). There is a direct correlation between the number of circulating platelets and the level of serum VEGF (Benoy et al., 2002). In addition, Wiesner et al. reported that; the platelet content of VEGF-A was significantly elevated in cancer patients compared to controls (Wiesner et al., 2010). In another pathway, tumor cells are prompted to aggregate in the circulation by homotypic adhesions among tumor cells and by heterotypic adhesions between tumor cells and platelets. This aggregation of platelets and tumor cells may play an important role in tumor cell survival (Fidler et al., 2003). In addition to these mechanisms, activated platelets in the tumor environment of ovarian cancer cells have been found to increase tumor cell invasion in a dose-dependent fashion (Holmes et al., 2009). According to these pathways, PLR and MPV, which can be easily evaluated by hematological analyzers, were used in the current study both to determine platelet functions and activation. As previously mentioned, larger platelets are more metabolically and enzymatically active than smaller platelets (Mangalpally et al., 2010) and strong evidence indicates that MPV is an important biological variable and that larger platelets are more metabolically and enzymatically active than smaller platelets (Dvorak et al., 1995). Both MPV and PLR also alleviate the effect of many common conditions that can alter the intravascular water component of blood, and hence the platelet count.

Neutrophils can promote tumor growth and metastasis by remodeling the extracellular matrix and they release reactants to proportionally inhibit the function of cytotoxic lymphocytes (Petrie et al., 1985). Preclinical studies have also indicated that neutrophils may act as tumor promoting leukocytes through TGF- β induced signal pathway (Suzuki et al., 2011). On the other hand, lymphocytes, usually CD3+T cells and NK cells, possess potent anti-cancer activities that could affect growth and/or metastasis in several cancers (Ohashi et al., 2006). Taken all together,

this evidence supports the explanation of the mechanisms as to why patients with lung cancer had high levels of NLR compared to the healthy subjects in the current study.

The major limitation of this study is that it is a retrospective, single-center study with a limited number of included patients and heterogenous group. Therefore, there may have been a failure to show the correlation between tumor stage and NLR and PLR. In the light of the studies cited above, it was expected that advanced stage patients might have high levels. However, to the best of our knowledge this is the first study analyzing MPV, NLR and PLR together and comparing lung cancer patients with healthy subjects. In addition, it is the first study evaluating these inflammatory parameters in small cell lung cancer. Similar to the current study, Serta Kilincalp et al. determined that MPV levels were significantly higher in pre-operative GC patients compared to healthy subjects (Kilincalp et al., 2013). More recently Dilek Unal et. al and Vildan Kaya et. al reported that pretreatment NLR measurements can predict patient prognosis in NSCLC patients (Kaya et al., 2013, Unal et al., 2013).

In conclusion, these PLR and NLR values will be used differently in clinical practice. The baseline NLR and PLR can be useful in stratifying LC patients before treatment, whereas the post-treatment values can be used for early evaluation of the treatment. This is only a preliminary study; larger prospective studies are required to confirm these findings. These cheap and easily available parameters could be useful in various cancers and might be more cost effective than other molecular methods.

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