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Systemic inflammation, TNM staging and survival in patients with lung cancer

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Abstract

English:

Background: *It is recognised that systemic inflammation plays an important role in the development and progression of lung cancer. Several affordable biomarkers could be used to evaluate systemic inflammation: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and erythrocyte sedimentation rate (ESR). These biomarkers may be linked with survival in lung cancer.*
Aim: *To assess the relation between systemic inflammation evaluated by NLR, PLR and ESR, tumour nodes metastasis (TNM) staging and negative outcome in lung cancer.*
Materials and methods: *Patients with lung cancer were classified (7th TNM lung cancer staging) into two groups: Group A (resectable stages) and Group B (nonresectable stages). Each group was divided into two subsets: survivors (As, Bs) and deceased (Ad, Bd) patients. Complete blood count (CBC) and ESR were determined. NLR and PLR were calculated. NLR, PLR and ESR values were compared between the two groups and their subsets.*
Results: *102 consecutive patients completed the protocol. In Group A (31 patients): NLR: 2.74 (0.87–12.94), PLR: 33.95 (21.61–416.66), ESR: 35 mm/h (6–135). Subgroup As: NLR: 2.36 (0.87–8.36), PLR: 138.82 (21.61–416.66), ESR: 15 mm/h (6–110). Subgroup Ad: NLR: 2.77 (1.25–12.94), PLR: 132.57 (41.11–371.17), ESR: 62 mm/h (11–135). In Group B (71 patients): NLR: 3.51(0.76–25.60), PLR: 170.37 (3.38–651.25), ESR:40 mm/h (3–120). Subgroup Bs: NLR: 1.40 (1.32–1.73), PLR: 112.89 (91.14–140.54), ESR: 31 mm/h (9–90). Subgroup Bd: NLR: 3.59 (0.70–25.60), PLR: 183.50 (3.38–651.25), ESR: 44 mm/h (3–120). NLR and PLR values were significantly higher (p: 0.04; p: 0.05) in Group B versus Group A. No significant difference was noted for ESR values between the two groups. In patients with nonresectable stages who were deceased (subgroup Bd), NLR and PLR values were significantly higher (p: 0.01; p: 0.03) versus survivals. In patients with resectable stages who were deceased (subgroup Ad), only the ESR value was significantly higher versus survivals.*
Conclusions: *Systemic inflammation assessed by affordable biomarkers as NLR and PLR is more prominent in advanced, nonresectable lung cancer. It may be a contributor, along with TNM staging, to the poor outcome of patients with nonresectable lung cancer.*
Clinical implication: *NLR and PLR may represent a valuable additional tool in the clinical management of patients with nonresectable lung cancer.*

Keywords

lung cancer • systemic inflammation • neutrophil-to-lymphocyte ratio • platelet-to-lymphocyte ratio

Relația dintre inflamația sistemică, stadializarea TNM și supraviețuire la pacienții cu diagnostic de cancer bronhopulmonar

Rezumat

Romanian:

Premize: *Inflamația sistemică are un rol important în apariția, proliferare, invazia, metastazarea, răspunsul la tratament și prognosticul cancerului bronhopulmonar. Raportul neutrofile/limfocite(NLR), raportul trombocite/limfocite(PLR), viteza de sedimentare a hematiilor(VSH), fibrinogenul și lățimea distribuției eritrocitare(RDW) reprezintă modalități de evaluare a inflamației sistemice în cancerul bronhopulmonar.*

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Scop: *Evaluarea relației dintre NLR, PLR si VSH ca biomarkeri ai inflamației sistemice, stadiile TNM ale cancerului bronhopulmonar și impactul asupra supraviețuirii pacienților.*
Materiale și metode: *Pacienți cu diagnostic de cancer bronhopulmonar, stadializat conform ediției a 7-a TNM, împărțiți conform stadiului bolii în două grupuri: Grupul A(stadii rezecabile: I-IIIA) și Grupul B (stadii nonrezecabile: IIIB-IV). Cele două grupuri au fost divizate în câte 2 subgrupuri: pacienți decedați (subgrupurile Ad, Bd) și supraviețuitori(subgrupurile As, Bs). S-au determinat: hemoleucograma (HLG),VSH, NLR, PLR. Rezultatele au fost comparate între cele două grupuri și subgrupurile lor.*
Rezultate: *Analiza a 102 pacienți consecutivi. În Grupul A (31): NLR:2,74(0,87- 12,94), PLR:133,95 (21,61-416,66), ESR:35 mm/h (6-135). Subgrupul As: NLR:2,36 (0,87- 8,36), PLR:138,82 (21,61-416,66), ESR:15 mm/h (6-110). Subgrupul Ad: NLR:2,77 (1,25-12,94), PLR:132,57 (41,11-371,17), ESR:62 mm/h (11-135). În Grupul B (71): NLR: 3,51(0,76-25,60), PLR: 170,37 (3,38-651,25), ESR:40 mm/h (3-120). Subgrupul Bs: NLR:1,40 (1,32-1,73), PLR:112,89 (91,14-140,54), ESR:31mm/h (9-90).Subgrupul Bd: NLR:3,59 (0,70-25,60), PLR:183,50 (3,38-651,25), ESR:44 mm/h (3-120). În Grupul B al pacienților cu stadii nonrezecabile, valorile rapoartelor NLR și PLR au fost semnificativ mai mari (p: 0.04, p: 0.05) decât în Grupul A (pacienți cu stadii rezecabile). Pacienții cu stadii nonrezecabile, decedați (subgrup Bd), au avut valori ale NLR si PLR semnificativ mai mari (p: 0.01, p: 0.03) comparativ cu pacienții supraviețuitori (Subgrup Bs).Nu același lucru s-a putut constata în cazul pacienților cu stadii rezecabile, decedați, la care doar valoarea VSH a fost semnificativ mai mare la decedați decât la cei supraviețuitori.*
Concluzie*:* *Inflamația sistemică evaluată prin biomarkeri accesibili precum raportul neutrofile limfocite (NLR) și raportul trombocite limfocite (PLR) este mai pronunțată în stadiile avansate, nonrezecabile ale cancerului bronhopulmonar și pare să influențeze negativ, alături de stadiul bolii, supraviețuirea pacienților. Atât raportul neutrofile limfocite (NLR) cât și raportul trombocite limfocite (PLR) ar putea avea aplicabilitate clinică în decizia terapeutică personalizată a pacienților cu stadii avansate ale cancerului pulmonar.*

Cuvinte-cheie

cancer bronhopulmonar • inflamatie sistemica • raport neutrofile-limfocite • raport trombocite-limfocite

Background

Lung cancer remains the most common malignancy worldwide, being the leading cause of cancer-related death, in both men and women, with most patients presenting advanced-stage disease at diagnostic, with low response at therapy (1, 2).

Non Small Cell Lung Cancer (NSCLC) accounts for 85% of primary lung cancers and despite great improvements in diagnostic technologies and progresses in developing new targeted treatment strategies according to specific tumour's features, the prognosis remains poor for patients with advanced-stage NSCLC.

Disease stage according to tumour nodes metastasis (TNM) classification, histology, gender, age and performance status are the most widely accepted prognostic factors, but not sufficiently effective for clinical use (3).

Thus, during recent years, an increasing number of studies have focused on novel and potential effective prognostic factors which may allow clinicians to use more appropriate therapeutic strategies.

Systemic inflammation through its cellular, molecular effectors and pathways plays an important role in the development and progression of many types of cancer, including lung cancer, and represents an open way for discovering accessible and feasible prognostic biomarkers for clinical use in an attempt to refine stratification of patients to personalised treatment and predict survival.

It is widely recognised that chronic inflammation through inflammatory cells and their cytokines and chemokines creates a microenvironment favourable to the development (by stimulating DNA cells damage) and progression (by ensuring promotion, proliferation, survival and migration off neoplastic cells) of tumours, called the "tumour microenvironment" (4).

On the other hand, tumour cells also contribute to the tumour microenvironment, producing various cytokines and chemokines that attract inflammatory cells: a diverse leukocyte population (neutrophils, mast cells, dendritic cells, macrophages and eosinophils) as well as lymphocytes (5).

Below is a brief description of the main inflammation "actors" which may explain their role in tumourigenesis and their prognostic value.

Neutrophils which are recruited into the tumour process, mainly by tumour necrosis factor alpha (TNFα), have a complex role in tumourigenesis by inhibiting apoptosis, promoting angiogenesis, cell proliferation and facilitating the formation of metastases.

There are two possible mechanisms through which neutrophils induce cell proliferation. One is direct cell-to-cell contact between the neutrophils and tumour cells (mediated by integrins like CD11/CD18 and intercellular adhesion molecules: ICAM-1) with subsequent activation of

the intracellular signalling pathways (e.g. mitogen-activated protein kinase [MAPK] – an important bridge in the switch from extracellular signals to intracellular responses) and induction of cellular proliferation. The second is neutrophil elastase ability to overactivate the phosphoinositide 3-kinase (PI3K) pathway (the most commonly activated signalling pathway in human cancer) with strong proliferative effects on lung cancer (6, 7).

The role of lymphocytes in cancer growth was also highlighted in many studies.

Tumour lymphocytic infiltration may suppress or promote tumour progression, depending on dominant subsets of lymphocytes.

T lymphocytes comprise 80% of tumour-infiltrating lymphocytes. Among these, $CD8^+$ cytotoxic lymphocytes are the effector arm of adaptive immunity which protect against tumour cells (8).

$CD\ 4^+$ T lymphocytes are also important, playing different and opposing roles in the tumour environment, according to their subsets. $CD4^+$ T helper cells optimise cytotoxic $CD8^+$ T cell response against tumour cells. In contrast, $CD4^+$ Treg (regulatory T cells) within tumours may downregulate the immune response, possibly through secretion of TGF-beta or by direct contact inhibition, being associated with tumour progression and worse prognosis in many types of cancers (9, 10).

Platelets are also recognised to be involved in the immune and inflammatory response, participating in regulation of mechanisms underlying a broad range of diseases, as cardiovascular disease, diabetes, sepsis and malignancies.

Activated platelets can contribute to tumour growth and invasiveness of cancer cells by releasing cytokines involved in angiogenesis (vascular endothelial growth factor: VEGF and platelet-derived growth factor: PDGF), promoting the formation of a capillary-like structure by endothelial cells, helping tumoral cells to escape immune surveillance (by interacting with fibrin and formation of platelet-fibrin-tumour cells) and enhancing tumour metastasis (3).

These findings could explain the association between elevated platelets and poor prognosis in malignant tumours, including lung cancer reported by several studies.

As mentioned above, there are several inflammatory cells with individual prognostic value, but an increasing body of evidence indicates that the levels of neutrophils, platelets and lymphocytes may function as a combined factor, which may more accurately reflect the inflammatory response, compared with a single factor.

Thus, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been developed as novel indicators of inflammation and potential prognostic biomarkers in many solid tumours, including lung cancer (11).

An elevated value of NLR and PLR may be associated with a poor prognosis in NSCLC (11, 12).

The aim of this study was to assess the relation between several affordable biomarkers of systemic inflammation, as NLR, PLR and erythrocytes sedimentation rate (ESR), TNM staging and negative outcome of patients with lung cancer.

Materials and methods

A retrospective observational study was carried out on 102 patients diagnosed with lung cancer between 2015 and 2016 in the IVth Pneumology Department of “Marius Nasta” Institute.

The analysed data (age, gender, body mass index [BMI], haemogram-derived parameters, leukocyte count, neutrophil count, lymphocyte count, platelet count [NLR and PLR], erythrocyte sedimentation rate: ESR, histopathological type and TNM tumour stage) were obtained from the medical file of the patients.

The informed consent signed at admission by patients allows us to use anonymised medical data for research and publication purposes.

Tumour stage based on clinical classification TNM (cTNM) was assessed for all patients according to the 7th edition of the UICC/AJCC TNM staging system.

The NLR and PLR ratios were calculated (absolute number of neutrophils and platelets divided by the lymphocytes number, as measured in the peripheral blood sample).

The deceased patients were identified using online Integreted Unique Information System (SIUI) of the National Health Insurance House (CNAS), 3 years after diagnoses (in 2018 and 2019).

Patients with lung cancer included in this study were divided into two groups: Group A comprising resectable and potentially resectable stages (IA, IB, IIA, IIB, IIIA) and Group B comprising nonresectable lung cancer stages (IIIB, IV).

Each group was divided into two subsets: survivors (As, Bs) and deceased (Ad, Bd) patients.

The NLR and PLR were calculated for each subset group and the values ware compared between the survivor and deceased patients.

Statistical analysis

The results were reported as mean ± standard deviation, median values/range or percentage. Statistical analysis of the data was performed using SPSS version 20.

Distribution of data was assessed using the Shapiro–Wilk test. Differences between numeric variables of the two groups were tested with the Independent samples Student’s *t*-test for continuous variables displaying normal distribution and the

Mann–Whitney *U* test was used for continuous variables not displaying normal distribution.

The results were considered statistically significant for $p < 0.05$. The diagrams used are bar charts.

Results and discussion

A total of 102 consecutive patients diagnosed with lung cancer were included in this study. The median age was 67 years (37–88), with the predominance of males (84.3%). History of smoking (active or former smokers) was encountered in 81.37% of patients and the median pack year value was 40 (3–100).

The majority of patients were diagnosed with NSCLC and the most common histological subtype was adenocarcinoma (62.3%), followed by squamous cell carcinoma (34.8%) and other subtypes (adenoid cystic lung carcinoma, pleomorphic carcinoma: squamous cell and giant cell carcinoma): 2.9%.

The median value of NLR was 3.33 (0.70–25.60) and for PLR it was 156 (3.38–651.25).

The tumour stage was assessed according to the 7th TNM clinical staging system and the patients were divided into two groups: *Group A* comprising resectable and potentially resectable stages (IA, IB, IIA, IIB, IIIA) and *Group B* comprising nonresectable lung cancer stages (IIIB, IV).

The baseline characteristics of the patients included in the two groups are shown in Table 1.

The two groups were similar in terms of age, pack-year history of tobacco use and histological subtypes (mainly NSCLC-adenocarcinoma followed by squamous). Statistically significant differences were found for NLR and PLR values, which were significantly higher in Group B compared with Group A (*p*: 0.04, respectively, *p*: 0.05), as shown in Figure 1.

No significant difference was found for ESR between the two groups.

The patients in Group B, with advanced stages of lung cancer, appear to have an increased systemic inflammation, assuming the fact that high values of NLR and PLR correlate with a higher degree of inflammation. The level of inflammation predict a poor outcome in advanced stages of lung cancer according to previous studies (13, 14).

According to the data referring to patient's survival obtained from the SIUI national database, each group (Groups A and B) was divided into two subsets comprising surviving (As, Bs) and deceased (Ad, Bd) patients.

The NLR and PLR were calculated for each subset group (as shown in Table 2) and the values ware compared between the survivor and deceased patients.

We found that in deceased patients with nonresectable/advanced stages (subset Bd), the values of NLR and PLR were significantly higher (*p*: 0.01, *p*: 0.03) than in the survivals (subset Bs) (Figure 2).

No statistically significant difference in the NLR and PLR values between the survivors and deceased patients was found in patients with resectable stages belonging to Group A, probably due to the fact that the magnitude of the systemic inflammation is less important in the early stages. Instead, in this group, ESR was significantly higher in the deceased versus survivals and could be a more appropriate method to evaluate the systemic inflammation's prognostic value in resectable lung cancer stages (Figure 3).

The median value of NLR in the subset Bd was 3.59, similar to other studies which reported pre-treatment cut-off values between 3.25 and 5, associated with a poor survival in patients with advanced NSCLC (15).

Further studies will be needed to establish a threshold value or a range for NLR that might allow clinicians to use this ratio as a prognostic biomarker in advanced stages of NSCLC.

The median PLR value in the subset Bd was 183.5, in accordance with the results of a meta-analysis (13) which demonstrated that elevated PLR (as a continuum value) might be a negative prognostic factor for patients with NSCLC, even if a definite PLR cut-off value has not yet been found. Thus, PLR may represent a promising prognostic biomarker for use in the clinical management of NSCLC patients.

There are some studies of patients with lung cancer which show that NLR values are elevated in patients with more advanced or aggressive disease (defined by an increased

Table 1. Characteristic of the patients with resectable (Group A) and nonresectable (Group B) lung cancer

102 patients	Age (years)	History of smoking (No, •/•)	PA (No)	Ne (/mm^3)	Ly (/mm^3)	Pl (/mm^3)	NLR	PLR	ESR (mm/h)
Group A (resectable stages) 31 (23 men)	**65** (51-83)	**23 74,2%**	**40** (3-100)	**6380** (2600-22.000)	**2000** (1020-13.600)	**294.000** (111.000-709.000)	**2,74** (0,87-12,94)	**133,95** (21,61-416,66)	**35** (6-135)
Group B (nonresectable stages) 71 (63 men)	**67** (37-88)	**60 84,5%**	**40** (4-90)	**6450** (1800-27.892)	**1800** (500-15.700)	**327.000** (23.000-661.000)	**3,51** (0,76-25,60)	**170,37** (3.38-651,25)	**40** (3-120)

PA: Pack year, Ne: Neutrophil, Ly: Lymphocyte, Pl: Plateles, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, ESR: Erythrocyte Sedimentation Rate.

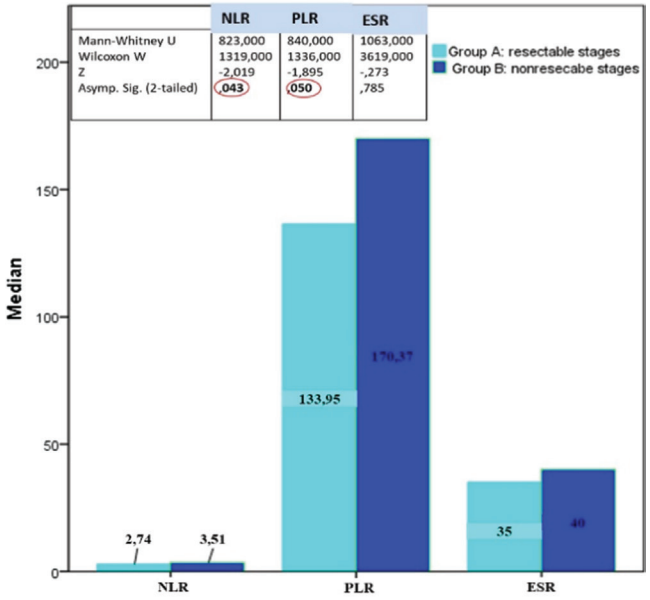


Figure 1. Difference between NLR, PLR and ESR values in resectable versus nonresectable stages.

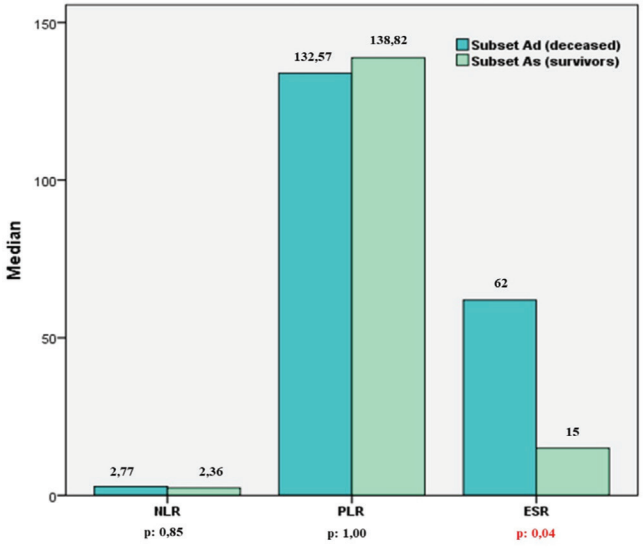


Figure 2. Differences in NLR, PLR and ESR values in the two subsets (deceased and surviving patients) of Group A (resectable stages of lung cancer).

Table 2. The value of NLR, PLR and ESR in the two subsets of Group A (n=31) and Group B (n=71)

	NLR	PLR	ESR (mm/h)
Subset As (survivors, n=11)	**2,36** (0,87-8.36)	**138,82** (21,61-416,66)	**15** (6-110)
Subset Ad (deceased, n=20)	**2,77** (1,25-12,94)	**132,57** (41,11-371,17)	**62** (11-135)
Subset Bs (survivors, n=8)	**1,40** (1,32-1,73)	**112,89** (91,14-140,54)	**31** (9-90)
Subset Bd (deceased, n=63)	**3,59** (0,70-26,60)	**183,50** (3,38-651,25)	**44** (3-120)

NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, ESR: Erythrocyte Sedimentation Rate.

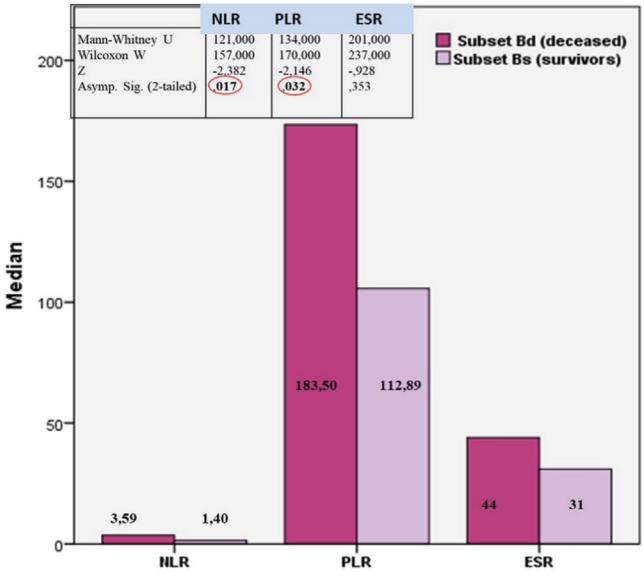


Figure 3. Differences in NLR, PLR and ESR values in the two subsets (deceased and surviving patients) of Group B (nonresectable stages of lung cancer).

tumour stage, nodal stage or presence of metastatic lesions); these patients may represent a particularly high-risk population (16).

In our study, we found that in advanced/nonresectable lung cancer stages (Group B), only deceased patients with metastatic stage (M_1) had significantly higher NLR and PLR values (p: 0.006, respectively, p: 0.009) than survivors patients. As for patients with non-metastatic advanced stages (M_0) the differences were not statistically significant between the deceased and survivors.

Conclusions

Systemic inflammation assessed by affordable biomarkers as NLR and PLR is more prominent in advanced, nonresectable lung cancer. It may be a contributor, along with TNM staging, to the poor outcome of patients with nonresectable lung cancer. This finding (high values of the two ratios) seems to be relevant, especially in patients with metastatic disease, potentially candidates for innovative biological therapies. Therefore, NLR and PLR may represent a valuable additional tool in the clinical management of patients with nonresectable metastatic lung cancer.

Further studies are needed to establish clear cut-off values for NLR and PLR and their role as individual prognostic biomarkers in advanced stages of lung cancer.

Disclosure

Data of this study were communicated as an oral presentation at the 25th edition of the National Congress of the Romanian Society of Pneumology, held in Poiana Brasov between October 31 and November 3, 2018.

Ethical approval

Inform consent was obtained from the patients in order to participate to the study and write the article.

Conflicts of interests

The authors declare that they have no conflicts of interest.

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