Use of neutrophil/lymphocyte ratio (NLR) and lymphocyte/monocyte ratio (LMR) as biomarkers in the differential diagnosis of malignant solitary pulmonary nodules

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ABSTRACT

Objective: Histopathological diagnosis of atypical lung nodules is often not possible in the preoperative period. This study evaluates the diagnostic value of neutrophil/lymphocyte ratio (NLR) and lymphocyte/monocyte ratio (LMR) as biomarkers in the differentiation of undiagnosed lung nodules.

Material and Methods: The study includes 91 patients (21 females, 70 males, mean age: 59.35 ± 11.85, age interval 20-81) operated on for lung nodules between September 2010 and September 2020. Age, gender, type of operation performed, histopathological type of the tumor, nodule size, SUVmax values measured on PET-CT, preoperative neutrophil/lymphocyte, and lymphocyte/monocyte ratios were analyzed retrospectively. These values were compared in patients with primary lung cancer (Group 1) and patients with secondary lung cancer, that is, patients with lung metastases from other organs (Group 2).

Results: NLR was statistically significantly higher in group 2 patients (N: 37)(3.38 ± 2.03). There was no statistically significant difference between the two groups in terms of LMR.

Conclusion: For lung nodules with unknown histopathological diagnosis, NLR values lower than 1.69 in preoperative complete blood count suggest primary lung cancer, and values above 2.92 suggest metastasis from other organs to the lung.

Keywords: Neutrophil/lymphocyte ratio; Lymphocyte/monocyte ratio; Biomarker; Pulmonary nodule; Malignant

INTRODUCTION

Solitary pulmonary nodules are lesions which located in the lung parenchyma and are smaller than 3 cm in diameter on radiological evaluation. In order for lesions in the lung parenchyma to be called solitary pulmonary nodules (SPN), these lesions should not be accompanied by atelectasis, lymphadenopathy, and pleurisy (1). Until proven otherwise, a nodule detected in the lung should be considered malignant and the examinations should be arranged accordingly. There has been a significant increase in the number of nodules detected in the lung, especially with the frequent use of thoracic computed tomography (CT). Although the characteristic features of the nodule on thorax CT inform us about the possibility of malignancy, this information is often insufficient. Identification and characterization of lung nodules are common in radiology (2). FDG uptake in Positron Emission Tomography (PET-CT) imaging provides information about the probability of malignancy in the nodule. Despite all examinations, the gold standard in diagnosis is tissue biopsy sampling. Unfortunately, a biopsy is not always possible due to the atypical location of the nodule. Many studies in recent years have suggested that systemic inflammation seen in malignancy patients may be associated with tumor burden, metastasis, invasion, and progression. One study showed that patients with malignancy may have neutrophilia and/or lymphopenia in peripheral blood evaluation (3). Considered more useful than neutrophil and lymphocyte counts, the neutrophil/lymphocyte ratio (NLR) is a newly developed marker for inflammation, and its elevation appears to be associated with a poor prognosis.

A routine hemogram test is an evaluation that can be applied to almost all patients after hospitalization, as it is inexpensive, minimally invasive, and provides predictions about many diseases. Recently, hemogram-derived neutrophil/lymphocyte ratios started to be used to determine the prognosis in patients followed for lung cancer (4).

The lymphocyte/monocyte ratio (LMR) is under investigation as another biomarker in patients followed up for lung cancer. Most of the research on LMR focuses on lung cancer prognosis. A meta-analysis of 20 studies showed that low pre-treatment LMR negatively affected overall survival and disease-free survival (5). However, to the best of our knowledge, there are no studies in the literature on the diagnostic role of NLR and LMR in the non-invasive histopathological evaluation of lung cancer and the preoperative differentiation of undiagnosed nodules as primary lung tumors or lung metastases from other organs.

In this study, we planned to calculate the neutrophil/lymphocyte ratio (NLR) and lymphocyte/monocyte ratio (LMR) in the preoperative complete blood test of patients with lung nodules and compare these ratios with the histopathology of the postoperative resected nodule. Accordingly, we aimed to evaluate the effectiveness of NLR and LMR as biomarkers in differentiating the nodule as a primary lung tumor or lung metastasis from other organs.

MATERIAL and METHODS

This study includes 91 patients (21 females, 70 males, mean age 59.35 ± 11.85, age interval 20-81) operated on between September 2010 and September 2020 for thorax computed tomography (CT) detected lesions smaller than 3 cm in the lung parenchyma that were not associated with atelectasis, lymphadenopathy or pleurisy. Patients were assessed retrospectively in terms of age, gender, type of operation performed, histopathological type of the tumor, size of the lung nodule, postoperative histopathological diagnosis, preoperative neutrophil, lymphocyte, monocyte counts, and ratios. All patients underwent preoperative complete blood count as well as thorax CT and PET-CT. The nodules were evaluated by a radiologist. All nodules in our study were solid. The patients were examined in 2 groups according to the histopathological diagnosis of the excised nodule. The nodules were evaluated as primary lung cancer in group 1 patients (N=54) and secondary lung cancer in group 2 (N=37), i.e., metastasis from other organs to the lung. In patients operated on for suspected lung metastasis, the primary tumor was under control. The neutrophil, lymphocyte, monocyte counts and the ratio of these values to each other were calculated in the preoperative complete blood count of the patients in both groups. All

hematological evaluations were performed in the same laboratory. Histopathological comparison of the resected lung nodules of the patients was performed with these ratios. NLR was obtained by dividing the number of neutrophils detected in the complete blood count in the preoperative period by the number of lymphocytes, and the LMR by dividing the lymphocyte number by the number of monocytes. The results were analyzed with statistical analysis programs, and the correlation between the hemogram-derived ratios and the postoperative histopathological type was evaluated. Preoperative lung function tests and arterial blood gas analysis were performed for all patients.

The study aimed to assess the clinical effectiveness of NLR and LMR in differentiating lung nodules as a primary lung tumor or lung metastasis from other organs.

The primary outcome of this study was to predict the histopathology of the nodule in patients who could not be biopsied.

Ethics committee approval was obtained for the study protocol. Informed consent for the operation was obtained from each patient in the study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Inclusion Criteria: Patients over the age of 18 with a lesion smaller than 3 cm in the lung parenchyma on thorax computed tomography (CT) were included in our study.

Exclusion Criteria: Patients with lung nodules larger than 3 cm and with atelectasis and pleurisy were not included in the study.

Statistical Analysis: Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk NY, USA) for Windows. Descriptive data were expressed as mean ± standard deviation (SD), median (min-max), number, and frequency. Variable distributions and conformity to normal distribution analyzes were checked with the Kolmogorov-Smirnov test. The Student's t-test was used for comparison between groups. The correlation between variables was evaluated using Pearson Correlation Analysis. ROC (Receiver Operating Characteristic) analysis was performed for cut-off values. P<.05 was accepted as the threshlold for statistical significance.

RESULTS

Group 1 patients (N: 54) consisted of 47 males, 7 females with a mean age of 62.7 (9.6) (range 23-81), and group 2 patients (N: 37) consisted of 23 males, 14 females, with a mean age of 54.4 (13.2) (between 20-73) (**Table 1**).

Table 1: Patients' Characteristics

	Group 1 (N:54)	Group 2 (N:37)	P Value
Age(years)	62.7±9.6	54.4±13.2	(p=0.001)
Gender			(p=0.005)
Male	47	23	
Female	7	14	
NLR	2.19 ± 0.95	3.38 ± 2.03	(p=0.001)
LMR	4.51 ± 2.01	3.76 ± 2.57	(p=0.12)
Size of the Nodule(mm)	20.05±7.4	15.02±5.79	(p=0.001)
SUVmax values	8.24±4.28	5.35±2.64	(p<0.001)
Wbc(10^3/ml)	7.43±2.65	6.89±1.87	(p=0.082)
Neutrophil(10^3/ml)	4.55±2	4.51±1.52	(p=0.11)
Lymphocyte(10^3/ml)	2.17±0.65	1.65±0.73	(p=0.063)
Monocyte(10^3/ml)	0.63±0.79	0.52±0.23	(p=0.094)

NLR: neutrophil/lymphocyte ratio, LMR: lymphocyte/monocyte ratio, Wbc: white blood cell
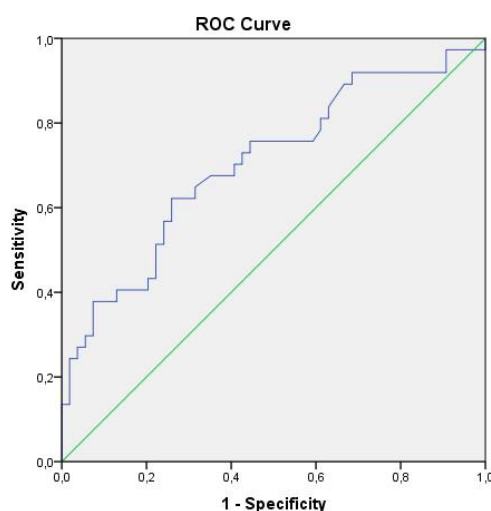
Figure 1: ROC(Receiver operating characteristic) analysis for NLR. AUC: 0.704, p=0.001, CI:0.592-0.815

Table 2: Cut-off values for NLR

	Cut-off	Sensitivity	Specificity	Youden's Index
Optimal	2.21	67.6	60.3	0.269
Max sensitivity	1.69	91.9	31.5	0.234
Max specificity	2.92	56.8	80.04	0.372

NLR: Neutrophil/lymphocyte ratio

The mean age in group 1 was higher than group 2 and this value is statistically significant.(p=0.001) The mean NLR was 2.19 (0.95) in group 1 and 3.38 (2.03) in group 2. There was a statistically significant difference in NLR values between the two groups, and the NLR was higher in group 2. For NLR, ROC analysis revealed AUC: 0.704, P= .001, CI: 0.592-0.815 (**Figure 1**).

Sensitivity and specificity analysis were performed for NLR at 3 different cut-off values. Cut-off was calculated as 1.69 (sensitivity 91.9%, specificity 31.5%), 2.92 (sensitivity 56.8%, specificity 80.04%), 2.21 (sensitivity 67.6%, specificity 60.3%) (**Table 2**).

The LMR was 4.51 (2.01) in group 1 and 3.76 (2.57) in group 2 (P=.12). There was no significant difference between the two groups. Although the neutrophil, lymphocyte, and monocyte counts were high in the first group, it was not statistically significant.

Nodule size is significantly different between two groups (p=0.001) and SUVmax is significantly different between two groups (p<0.001)

In group 1 patients, a moderately strong, significant, and positive correlation was observed between nodule size and SUVmax values (r=0.48, P=.001). There was no such relationship in Group 2.

DISCUSSION

Inflammation may occur intensely in cases such as tumor development, invasion, and metastasis. Although there are many articles on the relationship between lung cancer and NLR and LMR, these have generally focused on the prognosis of patients with lung cancer (4,5,6). Neutrophils have an important role in angiogenesis during tumorigenesis (7). Lymphocytes, on the other hand, have tumor growth-reducing effects in the body (8). Since most lung nodules are similar on thoracic CT imaging, radiological differentiation is difficult. Genetic analyzes and tumor marker evaluations are both expensive and incapable of distinguishing nodules. However, complete blood count to be used for preoperative NLR and LMR assessment is an easily accessible and inexpensive method.

This study reveals that high NLR values on the hemogram of a patient with a lung nodule may indicate lung metastasis of other organ malignancies. At the beginning of our study, we hypothesized that LMR would also be significant. Our study also concludes that LMR cannot be an effective marker for differentiating primary lung cancer and lung metastasis of other organ malignancies.

There was no significant difference between the two groups included in the study in terms of leukocyte, neutrophil, lymphocyte, and monocyte values. The NLR provides more information in detecting systemic inflammation than the evaluation of neutrophil and lymphocyte counts alone. These results show that systemic inflammation is more common in patients with metastasis (9,10). In accordance with the literature, since NLR was higher in the group operated on due to metastasis in our study, it is thought that systemic inflammation was higher as well. Although the primary tumor was under control, the high NLR detected in the group with metastasis may indicate that the effects of the primary tumor continued. In another study, the NLR was shown to be higher in patients with lung cancer compared to the normal population (11). High NLR values indicate that malignancies may be widespread throughout the body. A study conducted on patients with ovarian cancer reported that NLR values were higher in advanced-stage (Stage 3-4) patients than in early-stage (Stage 1-2) patients (12).

It is known that patients with a previous history of extrapulmonary malignancy are more likely to develop a new malignancy. Therefore, a lung nodule detected on the thorax CT of a patient with a malignancy history causes difficulties in diagnosis. In cases with atypical nodule localization, where histopathological examination cannot be performed, NLR to be calculated in hemogram test may be useful as a marker in preoperative diagnosis along with radiological nodule evaluation. NLR values <1.69 predict the histopathological result to be a lung-derived malignancy with a sensitivity of 91.9% and a specificity of 31.5%. Cut-off values of NLR less than 1.69 support primary lung cancer with much higher selectivity. On the other hand, in cases with an NLR above 2.92, it would be appropriate to interpret it as the metastasis of a previously detected malignancy with 56.8% sensitivity and 80.04% specificity. Although histopathological evaluation is the gold standard in the assessment of nodules, we believe that NLR will make a significant contribution to the diagnosis since hemogram evaluation is routinely performed for each patient.

While the immune system regulates tumor growth and metastasis, monocytes support tumor formation and metastasis (13). Multivariate analyzes in studies conducted for LMR in the literature show that LMR is an independent prognostic factor in NSCLC (14). Although our research determined higher LMR in group 1 patients than group 2 (4.51/3.76), the difference was not statistically significant to support its use as a biomarker in differentiating lung nodules as primary/metastatic. Studies with more patients may be beneficial to demonstrate the correlation between LMR and nodule histopathology.

A study comparing PET-CT-derived SUVmax values and nodule size determined that the SUVmax values of lung nodules larger than 1 cm, centrally located, and with irregular borders were significantly higher (15). Similarly, our study revealed a moderately strong, significant, and positive correlation between nodule size and SUVmax values in Group 1 patients. The lack of significant difference in SUVmax values between the two groups may be attributed to the relatively lower accuracy of PET-CT for solitary pulmonary nodules smaller than 3 cm.

CONCLUSION

Despite the limitations of our study, we think that NLR evaluation as a biomarker on hemogram, which is an inexpensive and easily accessible method, will be beneficial in the preoperative diagnosis of patients and prevent unnecessary large resections. We can also conclude that LMR should not be used as a marker in this evaluation. We think that studies with a larger number of patients on this subject will support our study.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. The Ethics Committee of the Necmettin Erbakan University Hospital approved the study.

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