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ORIGINAL ARTICLE

# Laboratory Parameters Predicting Brain Metastasis in Patients with Lung Cancer

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**OBJECTIVE**

Lung cancer (LC) is the leading cause of cancer death worldwide. Multiple studies have shown tumor progression and prognosis to be associated with immune status and nutritional condition. Alterations in blood lipid levels have been demonstrated to be a risk factor for LC. In the present study, we evaluate the effect of blood parameters on brain metastasis in LC.

**METHODS**

Patients identified with brain metastases during diagnosis or therapy and who subsequently underwent radiation therapy were included in the study. Patient characteristics, laboratory parameters, pathologic subtype, disease stage, treatment modalities, and outcome following treatment were recorded, and the patients' PFS and OS were calculated.

**RESULTS**

Univariate analysis revealed neutrophil, low-density lipoprotein (LDL), neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein levels to be significantly different between groups according to brain metastases. In a subgroup analysis based on cancer subtypes, LDL and lymphocyte levels were found to be significantly different in squamous cancer, while LDL was different in the undifferentiated subtype. OS was different in the NLR low and high groups, favoring the NLR low group (p=0.015; OS: 12 vs. 9 months), and the monocyte/lymphocyte ratio was significant in terms of OS favoring the low group with a cutoff value of 0.56 (p=0.002; OS: 13 vs. 9 months).

**CONCLUSION**

Our study identified differences in the inflammatory and lipid profiles of LC patients in terms of brain metastases and survival. Other than the literature, LDL levels were different among groups and may be considered a valid subject for future study.

**Keywords:** Brain metastasis; laboratory parameters; lipid profile; lung cancer.


## INTRODUCTION

Lung cancer (LC) is the leading cause of cancer death worldwide, with non-small-cell LC (NSCLC) and small-cell LC (SCLC) accounting for approximately 85% of all malign lung tumors.[1,2] Although rapid advances have been achieved in LC detection and treatment, 5-year survival rates are still inconclusive.[3] Multiple studies have

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shown tumor progression and prognosis to be associated with immune status and nutritional condition.[4–6]

Nearly, a quarter of all NSCLC patients are diagnosed at a locally advanced stage (stage III) and have a poor prognosis.[7] There are two treatment choices available for this condition: Induction chemotherapy followed by surgery, or concurrent chemoradiation therapy.[8,9] Even with advanced surgical techniques and post-operative consolidation chemotherapies, local recurrence rates are 20–40%.[10] Most of the remaining patients are diagnosed in the metastatic stage, resulting in palliative chemotherapy or radiation therapy.[7]

The previous studies have described inflammation-induced cancer progression leading to cancer cell proliferation and angiogenesis.[11] Accordingly, multiple blood inflammation markers are evaluated in different cancer types and stages that include neutrophils, lymphocytes, thrombocytes, and lipid and protein profiles, although the utility of these parameters is controversial.[12–15] Changing blood lipid levels have been identified as a risk factor for LC, and patients with LC tend to have low levels of low-density lipoprotein (LDL), HDL, and total cholesterol, while high triglyceride levels have been observed in blood samples.[15,16] Changes in blood lipid levels during therapy are considered to be an indicator of prognosis.[17,18]

The systemic inflammatory response in many solid tumors plays an essential role in development and progression.[19] A number of approaches to the measurement of systemic inflammation have been established, such as platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and neutrophil-to-lymphocyte ratio (NLR), and these parameters have been shown to be correlated with a poor prognosis in a variety of cancers, including NSCLC.[20–24]

Several hypotheses have been put forward to explain the relationship between prognosis and lymphocyte count. Lymphocytes are essential components of the immune system, being both controllers and effectors in response to tumor progression.[25] Low lymphocyte counts have been linked to decreased survival in cancer patients.[26–28] The systemic inflammatory response seen in many solid tumors plays an essential role in development and progression.[19] Several approaches to the measurement of systemic inflammation have been established, such as PLR, PNI, and NLR, and these parameters have been reported to be correlated with poor prognosis in a variety of cancers, including NSCLC.[20–24]

In the present study, we evaluate the effect of blood parameters on brain metastasis in LC.

## MATERIALS AND METHODS

### Study Participants

In this retrospective cohort study, the archival records of patients diagnosed with LC in the Eskişehir City Hospital Oncology Department were analyzed retrospectively between 2018 and 2020. Patients identified with brain metastases during diagnosis or therapy and who underwent radiation therapy were included in the study. Patient characteristics, lymphocyte-neutrophil count, hemoglobin, albumin, C-reactive protein (CRP) levels, lipid parameters, pathologic subtype, disease stage, treatment modality, and treatment outcomes were recorded, as well as the patients' calculated PFS and OS. The exclusion criteria were lack of adequate cancer diagnosis and follow-up.

### Ethics

Approval for the study was granted by the Eskişehir Osmangazi University Faculty of Medicine Institutional Board (March 02, 2021, dated and 06 numbered), and the study was carried out in accordance with the principles set out in the Declaration of Helsinki and all applicable regulations.

### Statistical Analysis

IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.) was used for the statistical analysis in the study. A Kolmogorov–Smirnov test was used to determine whether the data conformed to a normal distribution. Descriptive data were presented as either mean or median for continuous variables, while frequencies and percentages were reported for categorical variables. A Pearson $X^2$ test was used to assess the associations between categorical variables; OS and PFS curves were estimated using the Kaplan–Meier product-limit method; and a ROC analysis was performed to determine the optimal value.

## RESULTS

A total of 200 patients were enrolled in the study with a mean age of 65.6 years, of which 180 were male and 20 were female. The most common diagnoses were squamous cell carcinomas, adenocarcinomas, and undifferentiated lung carcinomas. The characteristics of the study population are summarized in Table 1. In a univariate analysis, neutrophil, LDL, NLR, and CRP levels were significantly different between groups splitted by brain metastases (Table 2). In a subgroup analysis of the different cancer subtypes, LDL and lymphocyte levels differed significantly in squamous cell cancer, while LDL was

**Table 1** The characteristics of the study population

| Features | n | % |
|---|---|---|
| Age (years), (mean, median) | 65.6, 66.0 | |
| Gender | | |
| Male | 180 | 90 |
| Female | 20 | 10 |
| PS | | |
| 0 | 10 | 5 |
| 1 | 61 | 30.7 |
| 2 | 87 | 43.7 |
| 3 | 38 | 19.1 |
| 4 | 3 | 1.5 |
| Diagnosis | | |
| Squamous | 80 | 41.5 |
| Adenocarcinoma | 51 | 26.4 |
| Undifferentiated | 33 | 17.1 |
| Small cell | 29 | 15 |
| Brain metastases | | |
| Yes | 131 | 65.8 |
| No | 68 | 34.2 |
| Received radiation to brain metastases | | |
| Yes | 68 | 93.2 |
| No | 5 | 6.8 |
| Stage at diagnosis | | |
| I | 2 | 1 |
| II | 11 | 6 |
| III | 71 | 35.5 |
| IV | 115 | 57.5 |
| Markers, mean value | | |
| Hemoglobin (g/dl) | 12.47 | |
| Neutrophil ($mm^3$) | 8460 | |
| Lymphocyte ($mm^3$) | 1260 | |
| Platelet ($mm^3$) | 273000 | |
| Monocyt ($mm^3$) | 670 | |
| Albumi (g/dl) | 3.52 | |
| CRP (g/dl) | 66.7 | |
| Markers, mean value | | |
| HDL | 41.5 | |
| LDL | 106 | |
| TG | 43 | |
| NLR | 11.6 | |
| Mono/HDL | 0.77 | |
| Mono/Lym | 304 | |
| Throm/Lym | 18.5 | |

PS: Performance score; CRP: C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; NLR: Neutrophil–lymphocyte ratio; Mono: Monocyte; Lym: Lymphocyte; Throm: Thrombocyte

different in the undifferentiated subtype. No significant differences were noted in the other histologic subtypes.

There was no optimal cutoff due to ROC analyses among groups. Median values were determined as cutoff, and groups were splitted due to these terms. The OS differed between the NLR low and high groups, favoring the NLR low group (p=0.015; OS: 12 vs. 9 months) (Fig. 1), while the monocyte/lymphocyte ratio was significant in terms of OS favoring the low group with a cutoff value of 0.56. (p=0.002; OS: 13 vs. 9 months) (Fig. 2). NLR has still had the prognostic effect in patients stratified according to brain metastases (p=004). The stage and performance status differed in terms of OS (p<0.001, p<0.001). In a multivariate analysis, no prognostic factor for OS was determined aside from performance status (p<0.001).

**Table 2** The comparison of the patient characteristics according to brain metastases

| Features | Brain metastases positive | Brain metastases negative | p |
|---|---|---|---|
| Age | 64 | 66 | 0.32 |
| Gender | 8/60 | 12/119 | 0.56 |
| Radiation therapy | 5/63 | N/A | N/A |
| Hemoglobin | 12.1 | 11.7 | 0.41 |
| Neutrophil | 9160 | 6850 | **0.022** |
| Lymphocyte | 975 | 1210 | 0.69 |
| Monocyte | 595 | 630 | 0.37 |
| Thrombocyte | 256000 | 260000 | 0.13 |
| LDL | 116 | 95 | **<0.001** |
| HDL | 43 | 37 | 0.40 |
| TG | 121 | 117 | 0.83 |
| NLR | 8.6 | 5.7 | **0.022** |
| Mono/HDL | 14.5 | 16.4 | 0.29 |
| Mono/Lym | 0.50 | 0.59 | 0.42 |
| Throm/Lym | 256 | 211 | 0.09 |
| CRP | 70.4 | 31.2 | **0.031** |
| Albumin | 3.6 | 3.5 | 0.51 |

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; NLR: Neutrophil–lymphocyte ratio; Mono: Monocyte; Lym: Lymphocyte; Throm: Thrombocyte; CRP: C-reactive protein

Lipid parameters were tested for correlation with inflammatory markers, revealing a significant inverse correlation between HDL and CRP (p<0.001, r: −0.28). A significant difference was noted in lymphocyte levels in the patients who had an initial brain metastasis at the time of diagnosis and late developers (p=0.02), and OS was also different for this group favoring late developers (p<0.001).

## DISCUSSION

In the present study, a difference was identified in the inflammatory markers of the brain metastatic and non-metastatic patients, and LDL, neutrophil, NLR, and CRP levels differed between the groups. Furthermore,

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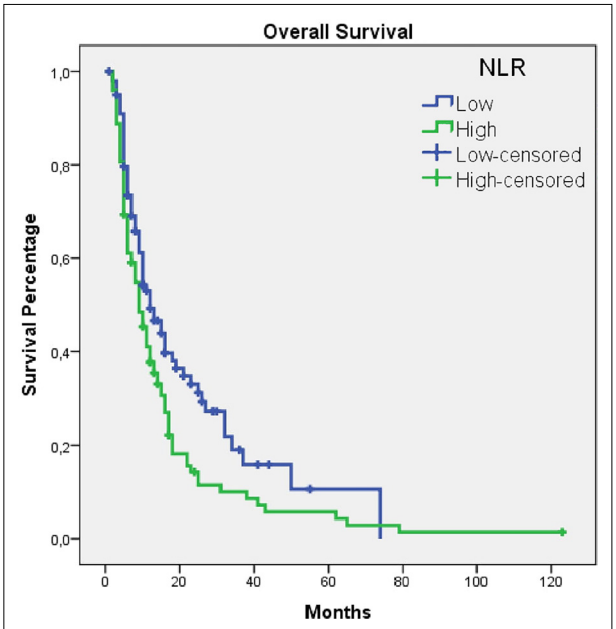


**Fig. 1.** Kaplan–Meier curves of patients according to neutrophil-to-lymphocyte ratio groups in general population.
NLR: Neutrophil-to-lymphocyte ratio.

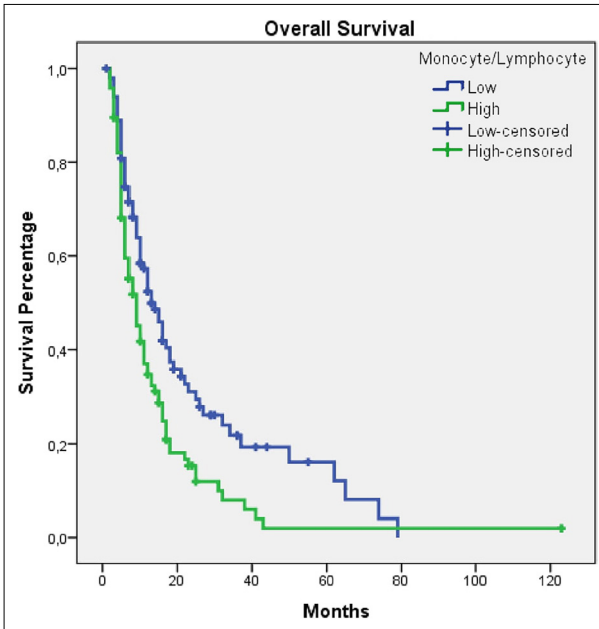


**Fig. 2.** Kaplan–Meier curves of patients according to monocyte/lymphocyte ratio group in general population.

the monocyte–lymphocyte ratio and NLR were found to be prognostic indicators of OS in the study population.

The SCLC metastasis site was found to influence mortality, and liver, bone, and brain metastasis decreased the duration of survival in this group.[29] In addition, high NLR values were reported to be related to early recurrences and reduced survival.[30] NLR values higher than 2.5 were found to be associated with decreased PFS in cancer patients.[31] A large-scale study determined a link between NLR>5 and poor prognosis in SCLC patients.[32] In another study, NLR was found significantly higher in the metastatic group.[33] In our research, NLR played a role in predicting brain metastasis and survival, concurring with the previous studies in the literature.

In patients with NSCLC, brain metastasis is associated with a decreased quality of life and survival. Multiple factors facilitate brain metastasis, one such factor being local and systemic immunosuppression.[34] The alterations in PD-1 expression lymphocytes have been shown to be a factor in the development of brain metastasis.[35] In another study, immune cells were found to be correlated with PS, decreased brain, and distant metastasis in EGFR mutant NSCLC.[36] The mechanisms of anti-cancer response with lymphocytes and the re-modeling effect of monocytes facilitate cancer proliferation and invasion, as demonstrated in the previous studies.[37,38] Although our study showed no difference in the effect of the monocyte–lymphocyte ratio on brain metastasis, a prognostic effect of monocyte–lymphocyte ratio OS was identified.

A previous study reported that Vitamin E levels alter the lipid profiles of cancer patients and increase oxidative stress, leading to cancer growth,[39] and other experimental studies support this suggestion. Alfa-tocopherol has been shown to play a therapeutic role under such circumstances.[40,41] Hyperlipidemia has been shown to be an adverse prognostic factor in stomach and prostate cancers, while studies of LC in this regard are limited.[30,31,42,43] Although all cholesterol types are reported to be lower in LC patients than in healthy controls, only HDL has been shown to have a prognostic effect. Low HDL levels are thought to be related to increased inflammatory cytokines such as CRP,[15] and this is supported by the present study. In contrast to other literature, however, our study revealed a significant between-group difference in LDL in brain metastasis.

## Limitations

The retrospective nature of this study decreased the data quality. Furthermore, some of the patients had brain metastases at the time of diagnosis, which was confusing for the mechanisms behind the metastatic process. Although most of the patients were treated for brain metastasis, five patients did not undergo RT.

## CONCLUSION

Our study identified a difference in the inflammatory and lipid profiles of LC patients in terms of brain metastases and survival. Other than the literature, LDL levels were different among groups and may be a subject of interest for future studies. Additional studies are needed to identify the parameters affecting brain metastases.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** All authors declared no conflict of interest.

**Ethics Committee Approval:** The study was approved by the Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (no: 06, date: 02/03/2021).

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**Authorship contributions:** Concept – F.T., İ.B., A.U.; Design – A.U.; Supervision – F.T., İ.B.; Funding – F.T., İ.B.; Materials – İ.B.; Data collection and/or processing – F.T., İ.B., A.U.; Data analysis and/or interpretation – F.T., İ.B.; Literature search – F.T.; Writing – F.T., İ.B.; Critical review – F.T., İ.B., A.U.

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