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Research Article

The Prognostic Significance of Lymphocyte-C-Reactive-Protein Ratio in Non-Small Cell Lung Cancer Patients Receiving Immunotherapy

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Abstract

Objectives: In this study, the significance of lymphocyte-C-reactive protein ratio (LCR) in indicating the prognosis/clinical course of patients with non-small cell lung cancer receiving immunotherapy was investigated.

Methods: All patients with non-small cell lung cancer who applied to Samsun Medicalpark Medical Oncology outpatient clinic between January 2020 and September 2022 and who received immunotherapy treatments after chemotherapy were included in this retrospective study. Total of 57 patients were included in this retrospective analysis. Clinical data of patients were recorded from patient files.

Results: This study was conducted with 57 patients with stage IV non-small cell lung cancer who received immunotherapy after failing to respond chemotherapy. The white blood cell, neutrophil, lymphocyte, monocyte and platelet counts of the patients who responded to the immunotherapy treatment significantly decreased after the treatment. When the pre-treatment values of patients who responded to and did not respond to immunotherapy were compared, pre-treatment white blood cell, neutrophil, C-reactive protein (CRP) and platelet to lymphocyte ratio (PLR) values were significantly higher in patients who did not respond to treatment. Pre-treatment serum albumin and LCR values were significantly higher in patients who respondedto immunotherapy.

Conclusion: This study demonstrated that higher LCR values before receiving immunotherapy may be a positive prognosis indicator in stage IV non-small lung cancer patients.

Keywords: lymphocyte-to-C-reactive protein ratio, lung cancer, biomarker, immunotherapy

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The leading cause of cancer-related deaths worldwide is the lung cancer, with approximately 85% being non-small cell lung cancer (NSCLC) and 15% being small cell lung cancer. Despite advances in efficient chemoradiotherapeutic regimens and novel molecule-targeting agents and immune checkpoint inhibitors interventions, the 5-year survival rate of NSCLC is only 2%. Currently, the most important indicator for prognosis includes the tumor, node, metastasis (Tumor Node Metastasis classification [TNM]) stage, which require chest computed tomography(CT) and cranial magnetic resonance imaging(MRI). Apart from imaging methods, there is a lack of novel biomarkers that will reflect the clinical course of the patients earlier which are of great value for clinical practice.Identifying and developing effective, novel and cost-effective prognostic markers may better guide the clinical evaluation and course of patients with lung cancer.[1,2]

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Accumulating evidence showed that inflammation is a critical main hallmark of cancer and has a crucial role in establishment and progression of tumors.[2-5] Among the inflammation markers, elevated C-reactive protein (CRP) has been shown to be a useful predictor for predicting poor survival in lung cancer patients. In all type of peripheral blood cells, lymphocytes are the most important cell group which establish cytotoxic responses to cancer cells and work against their proliferation, migration and invasion. Previous reports have demonstrated that various combinations of systemic inflammatory markers (e.g., serum C-reactive protein [CRP]), and immune markers (neutrophil count, platelet count, and total lymphocyte count [TLC]), can be used to generate predictive indexes such as the lymphocyte to CRP ratio (LCR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR).[6] Lymphocyte C-reactive protein ratio was found to be effective in demonstrating the prognosis in colon, rectum and breast cancer.[6-8] However, there are few studies showing the role of lymphocyte C-reactive protein ratio in lung cancer patients.[1,5] In addition, there is no study in the literature investigating the clinical role of lymphocyte c-reactive protein ratio in advanced lung cancer patients receiving immunotherapy. The aim of this study is to investigate whether the lymphocyte C-reactive protein ratio reflects the clinical course and can be utilized as a biomarker in non-small cell lung cancer patients receiving immunotherapy.

Methods

Study Group

This retrospective study included patients with non-small cell lung cancer with who applied to Samsun Medicalpark Medical Oncology outpatient clinic between January 2020 and September 2022. Stage IV non-small cell lung cancer patients who received immunotherapy treatments after chemotherapy. Total of 57 patients were identified and included in this retrospective study. The study was approved by Ondokuz Mayis University Clinical Research Ethics Committee (date: 25/01/2023, decision number: 2023/24) and the informed consent was waived due to the retrospective nature of the study.

This retrospective study included patients with stage IV non-small cell lung cancer who received immunotherapy. Our study was conducted by retrospectively scanning the data of patients who received immunotherapy in our Medical Oncology outpatient clinic between January 2020 and September 2022. A total of 57 patients were identified who received chemotherapy before immunotherapy and did not respond to chemotherapy. The patients received nivolumab or atezolizumab as immunotherapy. The study was approved by Ondokuz Mayis University Clinical Research Ethics Committee and the informed consent was waived due to the retrospective nature of the study.

Study Design

A data record form consisting of a total of questions, including demographic characteristics of patients, clinical characteristics, biochemical laboratory results were retrospectively filled in for each patient based on patient files and hospital records. The white blood cell, neutrophil, lymphocyte, platelet, and C-reactive protein values in the blood counts of the patients before receiving immunotherapy was recorded. In our outpatient clinic, patients were routinely evaluated by imaging methods in terms of progression in the 3rd month after immunotherapy. Accordingly, the patients were divided into 2 groups as responders and non-responders to immunotherapy. White blood cell, neutrophil, lymphocyte, thrombocyte, C-reactive protein values in the blood counts at the 3rd month of patients both responding to immunotherapy and not responding to treatment were recorded. The lymphocyte C-reactive protein ratio values of patients responders and non-responders were compared before and after immunotherapy.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The suitability of quantitative data to normal distribution was tested by Shapiro-Wilk test and graphical analysis. Since the lymphocyte C-reactive protein ratio before and after immunotherapy did not show normal distribution, the Wilcoxon test was used. Normally distributed age and BMI values were compared using the Student's t-test. The difference between the groups in terms of frequencies was compared using Fisher's test. A p value lower than 0.05 were considered statistically significant. Power analysis was done with G-power analysis according to study done by. Nishi et. al and the initial sample size to defect a significant difference was calculated as 42.

Lymphocyte C-reactive protein ratio was obtained by dividing the lymphocyte (µl) value by CRP (mg/l). NLR was calculated by dividing the neutrophil (µl) value by the lymphocyte (µl) number, and the PLR value was calculated by dividing the platelet (µl) number by the lymphocyte (µl) number.

Results

The retrospective study included 57 patients. There were 47 (82.5%) male and 10 (17.5%) female patients. The mean age of the patients was 65.9±11.1 years (34-85 years). While 46 (80.7%) of 57 patients responded to immunotherapy, 11 (19.3%) patients did not respond to treatment and progressed. Pre-treatment and post-treatment laboratory values of patients who responded to immunotherapy treatment are shown in Table 1. Pre-treatment WBC, neutrophil, lymphocyte, monocyte and platelet counts were significantly higher than post-treatment values in patients responding to immunotherapy. There was no statistically significant difference between pre-treatment and post-treatment hemoglobin, CRP, albumin, LDH, LCR, NLR, and PLR values.

Pre- and post-treatment laboratory results of patients who do not respond to immunotherapy treatment and progress are shown in Table 2. Pre-treatment monocyte levels were significantly higher than post-treatment levels in patients who did not respond to immunotherapy. There was no statistically significant difference between pre-treatment and post-treatment WBC, neutrophil, lymphocyte, platelet, hemoglobin, CRP, albumin, LDH, LCR, NLR, and PLR values.

In Table 3, laboratory values and demographic characteristics of patients who responded and did not respond to immunotherapy were compared. Pre-treatment WBC, neutrophil, CRP and NLR values were significantly higher in patients who did not respond to treatment. Albumin and LCR values were significantly lower (Table 3). There was no statistically significant difference between patients who responded and

Table 1. Pre- and post-treatment laboratory values of patients responding to immunotherapy

	Pre-treatment	Post-treatment	p
WBCs (µl)	7095 (5505-9467)	6405 (3063-5298)	0.004
Neutrophils (µl)	4890 (3572-6165)	4330 (3062-5798)	0.046
Lymphocytes (µl)	1395 (1028-1890)	1000 (630-1575)	0.019
Monocytes (µl)	735 (575-862)	530 (360-770)	<0.0001
Hemoglobin (g/dl)	11.65 (10.3-13.33)	11.8 (10.58-13.0)	0.358
Platelets (x10^3 µl)	250 (200-332)	223 (189-299)	0.016
CRP (mg/l)	3.24 (0.77-10.28)	3.13 (1.16-9.22)	0.242
Albumin (g/dl)	4.08 (3.65-4.29)	4.0 (3.58-4.3)	0.356
LDH (U/l)	234 (173-271)	237 (191-308)	0.611
LCR	360 (126-1977)	292 (110-983)	0.454
NLR	3.68 (2.6-5.12)	3.73 (2.46-7.08)	0.164
PLR	190 (131-272)	250 (125-372)	0.066

WBCs: White blood cell count; CRP: C-reactive protein; LDH: Lactate dehydrogenase; LCR: Lymphocyte to C-reactive protein ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

Table 2. Pre- and post-treatment laboratory values of patients who did not respond to immunotherapy

	Pre-treatment	Post-treatment	p
WBCs (µl)	9900 (8390-17650)	9570 (6700-17000)	0.646
Neutrophils (µl)	8100 (6260-14600)	7500 (4390-13250)	0.508
Lymphocytes (µl)	1160 (970-1230)	950 (490-1140)	0.169
Monocytes (µl)	610 (540-880)	520 (300-580)	0.028
Hemoglobin (g/dl)	11.90 (8.8-12.7)	10.2 (9.6-12.4)	0.799
Platelets (x10^3 µl)	290000 (206-319)	225000 (185-256)	0.139
CRP (mg/l)	38.7 (5.1-60.1)	10.0 (6.75-12.7)	0.424
Albumin (g/dl)	3.58 (3.24-3.62)	3.86 (3.1-3.9)	0.386
LDH (U/l)	318 (180-426)	369 (210-660)	0.248
LCR	34 (19-233)	79 (35-114)	1.0
NLR	9.83 (4.34-15.05)	6.58 (4.1-17.7)	0.386
PLR	216 (187-282)	246 (163-430)	0.386

WBCs: White blood cell count; CRP: C-reactive protein; LDH: Lactate dehydrogenase; LCR: Lymphocyte to C-reactive protein ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

Table 3. Comparison of pre-treatment laboratory values and demographic characteristics of patients who responded and did not respond to immunotherapy

	Patients who responded to immunotherapy	Patients who did not respond to immunotherapy	p
Age (years)	65.7±10.6	66.7±13.9	0.790
Gender (M/F)	(38/8)	(9/2)	1.0
BMI (kg/m^2)	25.4±4.3	23.3±1.9	0.025
Smoking (yes/no)	(35/11)	(8/3)	0.550
WBCs (µl)	7095 (5505-9467)	9900 (8390-17650)	0.009
Neutrophils (µl)	4890 (3572-6165)	8100 (6260-14600)	0.003
Lymphocytes (µl)	1395 (1028-1890)	1160 (970-1230)	0.132
Monocytes (µl)	735 (575-862)	610 (540-880)	0.585
Hemoglobin (g/dl)	11.65 (10.3-13.33)	11.90 (8.8-12.7)	0.473
Platelets (x10^3 µl)	250 (200-332)	290 (206-319)	0.762
CRP (mg/l)	3.24 (0.77-10.28)	38.7 (5.1-60.1)	0.013
Albumin (g/dl)	4.08 (3.65-4.29)	3.58 (3.24-3.62)	0.001
LDH (U/l)	234 (173-271)	318 (180-426)	0.108
LCR	360 (126-1977)	34 (19-233)	0.005
NLR	3.68 (2.6-5.12)	9.83 (4.34-15.05)	0.003
PLR	190 (131-272)	216 (187-282)	0.196

WBCs: White blood cell count; CRP: C-reactive protein; LDH: Lactate dehydrogenase; LCR: Lymphocyte to C-reactive protein ratio; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet to lymphocyte ratio; BMI: Body Mass Index.

did not respond to immunotherapy in terms of age, gender, number of patients who were smoking, lymphocytes, monocytes, hemoglobin, platelet, LDH, and PLR values.

Discussion

In this study, patients with stage IV non-small cell lung cancer who received immunotherapy after failing to respond chemotherapy were investigated in terms of prognostic significance of lymphocyte-to-C-reactive protein ratio.

Systemic inflammation mediators, such as lymphocytes and CRP, have been recognized as important biomarkers of tumor initiation, growth, progression and metastasis. Lymphocytes act as safeguards against tumors by identifying and destroying malignant cells. Dusseller et al. underlined the central role of neutrophils in tumor aggressiveness and the inability of nivolumab to stop and overturn neutrophils' pro-tumor action by demonstrating that a major host neutrophil inflammation indicated by ΔNLR > 1 characterized the early progressors and shortened overall survival after starting nivolumab.[3] CRP is one of the phenotype acute-phase proteins induced by hepatocytes, which is regulated by interleukin-6. High levels of CRP have been reported to be associated with an increased risk of lung cancer, colorectal cancer and esophageal cancer.[3]

Here, it is shown that the white blood cell, neutrophil, lymphocyte, monocyte and platelet counts of the patients who responded to the immunotherapy treatment significantly decreased after the treatment. Some recent studies emphasized that early changes of these simple hematological parameters help to better distungish responder from non-responder patients. Guida et al. showed that variations in platelets, WBC, neutrophils, and lymphocytes after a cycle of immunotherapy strongly influenced the progression-free survival of malign melanoma patients.[9] They also emphasized that early variations during treatment may serve as a simple monitoring tool to evaluated the continuation of therapy in the case of uncertain clinical outcomes.[9]

There was no significant difference in LCR, NLR, PLR values before and after treatment in patients who did not respond to immunotherapy. When the pre-treatment values of patients who responded to and did not respond to immunotherapy are compared, pre-treatment white blood cell, neutrophil, CRP and PLR values were significantly higher in patients who did not respond to treatment. In their meta-analysis, Han et al. reported that high baseline CRP levels cancer patients may be an indicator for worse overall survival and progression-free survival of cancer patients treated with immune checkpoint inhibitors.[10] In another study, Lee et al. showed that increased pre- and post-treatment peripheral lymphocyte count was associated with favorable PFS and OS with non-small cell lung cancer patients treated with immune checkpoint inhibitors.[11] Previous studies have shown that a high NLR and elevated PLR are associated with poor outcomes in lung cancer patients receiving immuno-

therapy.[12,13] Thus, pre-treatment neutrophilia and lymphopenia tended to be associated with poor prognostic factor for overall survival, relapse, or metastasis in solid tumors.

While the LCR value measured after treatment does not indicate the prognosis of the non-responder patients, pre-treatment serum albumin and LCR values were significantly higher in patients who responded to immunotherapy. He et al. showed that pretreatment LCR is a promising biomarker for first-line progression-free survival and overall survival in patients with lung cancer.[5] Lee et. al also showed that pretreatment nutritional status with low albumin levels were associated with lower overall survival in lung cancer patients who receive checkpoint inhibitors.[14] Overall, consistent with the findings from other studies,[15] this study demonstrated that higher pre-treatment LCR values, as a result of high lymphocyte counts and lower CRP levels can be a positive prognostic indicator in stage IV non-small lung cancer patients receiving immunotherapy.

This initial exploratory study has some limitations owing to its retrospective nature, and low sample size. Furthermore, because a single ratio only catches a frozen glimpse from the time, it is difficult to attribute it to the immune system's perpetual movement. Future multi-center prospective studies on larger populations with more repetitive measurements will help to better verify and understand the significance of novel prognostic markers.

Conclusion

This study demonstrated that higher LCR values before receiving immunotherapy may be a positive prognosis indicator. These results may help to design further studies that indicates more accurate prognostic markers to establish novel follow-up strategies in patients with non-small cell lung cancer. Future well-designed studies will provide better insights into the predictive and prognostic role of the ratio of lymphocytic count along with C-reactive protein levels.

Disclosures

Ethics Committee Approval: This study was performed in keeping with the principles outlined in the Declaration of Helsinki and approved by Ondokuz Mayis University Clinical Research Ethics Committee (date: 25/01/2023, decision number: 2023/24).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Zhao T. (2022). Prognostic assessment of C-reactive protein and neutrophil to lymphocyte ratio in patients with non-small cell lung cancer. Wiener klinische Wochenschrift, 134(19-20), 705–711. https://doi.org/10.1007/s00508-022-02049-4
2. Svaton, M., Zemanova, M., Skrickova, J., Jakubíková, L., Kolek, V., Kultan, J., ... & Pesek, M. (2018). Chronic inflammation as a potential predictive factor of nivolumab therapy in non-small cell lung cancer. Anticancer Research, 38(12), 6771-6782.
3. Dusselier, M., Deluche, E., Delacourt, N., Ballouhey, J., Egenod, T., Melloni, B., ... & Vergnenègre, A. (2019). Neutrophil-to-lymphocyte ratio evolution is an independent predictor of early progression of second-line nivolumab-treated patients with advanced non-small-cell lung cancers. PloS one, 14(7), e0219060.
4. Khunger, M., Patil, P. D., Khunger, A., Li, M., Hu, B., Rakshit, S., ... & Velcheti, V. (2018). Post-treatment changes in hematological parameters predict response to nivolumab monotherapy in non-small cell lung cancer patients. PloS one, 13(10), e0197743.
5. He Y, Gong R, Peng KW, Liu LZ, Sun LY, Wang HY. Lymphocyte-to-C-reactive protein ratio is a potential new prognostic biomarker for patients with lung cancer. Biomark Med. 2020 Jun;14(9):717-726. doi: 10.2217/bmm-2019-0452.
6. Nishi M, Shimada M, Tokunaga T, Higashijima J, Yoshikawa K, Kashihara H, Takasu C, Ishikawa D, Wada Y, Eto S, Yoshimoto T. Lymphocyte to C-reactive protein ratio predicts long-term outcomes for patients with lower rectal cancer. World J Surg Oncol. 2021 Jul 6;19(1):201. doi: 10.1186/s12957-021-02319-x.
7. Ou, W., Zhou, C., Zhu, X., Lin, L., & Xu, Q. (2021). Prognostic Significance of Preoperative Lymphocyte-to-C-Reactive Protein Ratio in Patients with Non-Metastatic Colorectal Cancer. OncoTargets and therapy, 14, 337.
8. Wang L, Zhang YL, Jiang C, Duan FF, Yuan ZY, Huang JJ, Bi XW. Novel Signatures Based on the Lymphocyte-to-C-Reactive Protein Ratio Predict the Prognosis of Patients with Early Breast Cancer: A Retrospective Study. J Inflamm Res. 2022 Jul 13;15:3957-3974. doi: 10.2147/JIR.S364284.
9. Guida, M., Bartolomeo, N., Quaresmini, D., Quaglino, P., Madonna, G., Pigozzo, J., Di Giacomo, A. M., Minisini, A. M., Tucci, M., Spagnolo, F., Occelli, M., Ridolfi, L., Queirolo, P., De Risi, I., Valente, M., Sciacovelli, A. M., Chiarion Sileni, V., Ascierto, P. A., Stigliano, L., & Strippoli, S. (2022). Basal and one-month differed neutrophil, lymphocyte and platelet values and their ratios strongly predict the efficacy of checkpoint inhibitors immunotherapy in patients with advanced BRAF wild-type melanoma. Journal of translational medicine, 20(1), 159. https://doi.org/10.1186/s12967-022-03359-x
10. Han C-L, Meng G-X, Ding Z-N, Dong Z-R, Chen Z-Q, Hong J-G, Yan L-J, Liu H, Tian B-W, Yang L-S, Xue J-S and Li T (2022) The Predictive Potential of the Baseline C-Reactive Protein Levels for the Efficiency of Immune Checkpoint Inhibitors in Cancer Patients: A Systematic Review and Meta-Analysis. Front. Immunol. 13:827788. doi: 10.3389/fimmu.2022.827788
11. Lee, Y.J., Park, Y.S., Lee, H.W. et al. Peripheral lymphocyte count as a surrogate marker of immune checkpoint inhibitor therapy

outcomes in patients with non-small-cell lung cancer. Sci Rep 12, 626 (2022). https://doi.org/10.1038/s41598-021-04630-9

12. Hong, X. et al. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J. Exp. Med. 236, 297–304. https://doi.org/10.1620/tjem.236.297 (2015).
13. Wang, H., Li, C., Yang, R., Jin, J., Liu, D., & Li, W. (2022). Prognostic value of the platelet-to-lymphocyte ratio in lung cancer patients receiving immunotherapy: A systematic review and meta-analysis. PloS one, 17(5), e0268288. https://doi.org/10.1371/journal.pone.0268288
14. Lee, C. S., Devoe, C. E., Zhu, X., Fishbein, J. S., & Seetharamu, N. (2020). Pretreatment nutritional status and response to checkpoint inhibitors in lung cancer. Lung cancer management, 9(2), LMT31. https://doi.org/10.2217/lmt-2020-0008
15. Zhang, H. Y., Xie, H. L., Ruan, G. T., Zhang, Q., Ge, Y. Z., Liu, X. Y., Tang, M., Song, M. M., Lin, S. Q., Yang, M., Zhang, X. W., Xu, H. X., Song, C. H., & Shi, H. P. (2022). Lymphocyte to C-reactive protein ratio could better predict the prognosis of patients with stage IV cancer. BMC cancer, 22(1), 1080. https://doi.org/10.1186/s12885-022-10145-x