EJMI

DOI: 10.14744/ejmi.2023.21564
EJMI 2024;8(1):28–34

Research Article

Combined LDH Albumin Score (CLAS) and Neutrophil-Lymphocyte Ratio (NLR) are Predictive for Survival in Patients with Metastatic Non-Small Cell Carcinoma Treated with Nivolumab as Monotherapy

Elif Sahin

Department of Medical Oncology, Kocaeli City Hospital, Kocaeli, Türkiye

Abstract

Objectives: It was aimed to investigate the prognostic significance of neutrophil-to-lymphocyte ratio(NLR), platelet-to-lymphocyte ratio(PLR), systemic immune-inflammation index(SII), and Combined LDH Albumine Score(CLAS) in metastatic non-small cell lung cancer(mNSCLC) patients receiving nivolumab.

Methods: Sixty-five mNSCLC patients who received nivolumab as monotherapy and had a follow-up file in Kocaeli City Hospital were analyzed retrospectively. ROC-curve analysis and median values were used to determine the cut-off. The relationship between overall survival(OS), progression-free survival(PFS) and clinical and laboratory parameters was evaluated by multivariate analyses.

Results: Mean age was 62.5±4.5 years, more than half(66%) had denovo metastatic disease. Median follow-up time was 22 (IQR:12-33),median PFS was 6 (95% CI 3.4–8.6),and median OS was 9 (95% CI 5.2–18.1) months. NLR≥3.2, PLR≥199, and SII≥776 were considered as elevated levels. No factor other than NLR could be identified as having an impact on PFS (p=0.015,[HR]:0.46,95%CI: 0.23–0.91). Univariate analyses showed that high baseline NLR, low baseline albumin and CLAS< 2 (0-1) were a significant risk factors for poor OS, but only CLAS<2 was found as an independent prognostic factor for OS in multivariate analyses (p=0.013,[HR]:0.68,95%CI:0.42–0,95).

Conclusion: NLR and CLAS were predictive for survival in patients with NSCLC receiving nivolumab.This is the second study on CLAS in the literature.

Keywords: Lung Cancer, Nivolumab, Combined LDH Albumin Score (CLAS), Neutrophil-lymphocyte ratio (NLR), Systemic immune-inflammation index (SII)

Cite This Article: *Sahin E. Combined LDH Albumin Score (CLAS) and Neutrophil-Lymphocyte Ratio (NLR) are Predictive for Survival in Patients with Metastatic Non-Small Cell Carcinoma Treated with Nivolumab as Monotherapy. EJMI 2024;8(1):28–34.*

Lung cancer is the most common cancer in men worldwide and the leading cause of cancer death (1.8 million deaths) in both sexes.[1] Lung cancer is classified into two main groups as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) according to the histology of the tumor. NSCLC is the most common (85-90%) group.[2] Without targetable mutation, 5-year survival is 50-82% in early-stage NSCLC and 6-10% in metastatic NSCLC (mNSCLC).[3] In the last decade, the 5-year survival in mNSCLC has increased to 24% due to the use of immunotherapies in the first series.[4]

Nivolumab, one of the immune checkpoint inhibitors, inhibits PD-1 receptors and activates the immune system. In 2015, in patients with mNSCLC who progressed after platinum-based chemotherapy, Nivolumab demonstrated a median overall survival of 12.2 months versus 9.4 months.[5] In the first serial, it can be used in combination with ipi-

Address for correspondence: Elif Sahin, MD. Department of Medical Oncology, Kocaeli City Hospital, Kocaeli, Türkiye
Phone: +90 506 808 08 67 **E-mail:** dr_elifsahin48@hotmail.com

Submitted Date: August 13, 2023 **Accepted Date:** October 13, 2023 **Available Online Date:** October 26, 2023

limumab and chemotherapy but in the second serial, it has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as monotherapy use.[4,6] Finding a marker that can predict the effectiveness of these drugs, which are very costly, is very important both to reorganize the treatment options of the patient and not to put an unnecessary burden on the country's economy.

Recently, immune inflammation indices such as neutrophil (N) to lymphocyte (L) ratio (NLR), platelet (P) to lymphocyte ratio (PLR), systemic immune inflammation index (SII = N x P / L) and combined LDH albumin score (CLAS) were investigated and found to be associated with decreased survival in some cancers.[7-10] CLAS is a scoring system first proposed by Daher et al. in 2021 and includes four different prognostic groups : high LDH + low alb (CLAS 0), low LDH + low alb (CLAS 1), high LDH + high alb (CLAS 2), low LDH + high alb (CLAS 3). In this study, patients classified as CLAS 0 showed the lowest survival. After this study with 35 patients, there was no study conducted on a larger patient group investigating the effect of CLAS on cancer patients.

In our study, we aimed to analyze the prognostic significance of NLR, PLR, SII, and CLAS (about which there is no data except for one study in the literature) in mNSCLC patients using Nivolumab.

Methods

The documents of patients with metastatic non-small cell lung cancer diagnosed between January 2016 and July 2023, who were followed up in the Kocaeli City Hospital oncology clinic, were retrospectively analyzed. Patients with missing data or targetable mutations were excluded from the study. Only those receiving nivolumab as monotherapy were included in the study. Immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) 1.1 criteria were used for radiological response evaluation. Inflammation scores were calculated with the following equations; NLR = N/L, PLR = P/L, SII = [N x P]/L. SPSS package program version 22.0 (IBM Inc., Armonk, NY, USA) was used for statistical analysis. Conformity to normal distribution was evaluated with Kolmogorov Smirnov test and numerical variables were given as mean±standard deviation, median (%25-75) and frequency (percentiles). Chi-square test was used for categorical variables to evaluate the differences between groups. The receiver operating curve (ROC) analysis was used to find the cut-off values of inflammation scores. However, p value could not reach significance in ROC analysis for both NLR, PLR and SII. For this reason, median values were used as cut-off values in all of them. Patients with CLAS 0 and 1 were grouped as low CLAS, and those with 2 and 3 as high CLAS. The overall survival (OS) time was defined as the time from the start of nivolumab therapy to the last follow-up and/or death, whereas the progression-free survival (PFS) time was defined as the time from the start of nivolumab to disease progression and/or death. Survival analyses were performed using Kaplan-Meier methods. Cox regression analyzes were used for the effects of inflammation scores on progression-free survival and overall survival. Hazard ratios (HR) were calculated with 95% confidence intervals (CI) and $p<0.05$ was considered sufficient for statistical significance in two-way tests.

Results

A total of 73 patients' data were reviewed, and 8 patients were excluded due to lack of data. The mean age of 65 patients was 62.5±4.5 years and 89% of them were male. A majority (65%) had one or more comorbidity and had (68%) a smoking history. Twenty-eight (38%) patients had mediasten/lung irradiation. The mean body mass index of the cohort was 25.8±4.4. More than half (66%) had denovo metastatic disease. Bone metastases were present in 61% of the patients, brain metastases in %9 and visceral metastases in 42%. Eighty-eight percent of the cohort had a Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Histologically, the most common subtypes were squamous cell cancer (49%) and adenocancer (40%). The PDL-1 level was unknown in the vast majority (89%) of patients. In the metastatic setting, the most commonly (%50) prescribed treatments before nivolumab were paclitaxel plus carboplatin. General characteristics of the cohort are summarized in Table 1.

In the ROC analysis performed to find the cut off value for NLR PLR and SII, the p value could not reach significance ($p=0.123$; $p=0.299$; $p=0.613$ respectively). Therefore, median values were considered as cut-off values and NLR ≥ 3.2, PLR ≥ 199, and SII ≥ 776 were evaluated as elevated levels.

Median follow-up time was 22 (12-33) months. In the metastatic setting, median time to nivolumab treatment was 9 (5-16) months. The best radiological response to nivolumab treatment was complete response (CR) in 7 (11%) patients, partial response (PR) in 23 (35%) patients, and stable disease (SD) in 18 (28%) patients. In 10 cases, the disease did not respond to treatment from the beginning and developed progressive disease (PD).

The most common side effects related with therapy were fatigue (23%), nausea (18%) and decreased appetite (18%). Grade 3 or higher side effects were seen in 20% of the patients. The most common high grade serious adverse effect is fatigue (12%).

Table 1. Baseline characteristics of the cohort

Characteristic	n (%)
Gender	
Male	58 (89)
Female	7 (11)
Mean age (year)	62.5±4.5
Comorbidity	
Yes	42 (65)
No	23 (35)
Mean BMI (kg/m^2)	25.8±4.4
Smoking history	
Yes	44 (68)
No	21 (32)
Radiotherapy history	
Yes	28 (38)
No	37 (62)
Histological subtype	
Adeno Ca	26 (40)
SCC	32 (49)
NOS	7 (11)
Metastatic situation	
De novo metastatic	43 (66)
Subsequently	22 (34)
ECOG performance score	
0	30 (46)
1	27 (42)
2	8 (12)
Sites of metastasis	
Bone	40 (61)
Visceral	
Lung	56 (87)
Liver	14 (22)
Brain	6 (9)
Surrenal	13 (20)
Number of metastasis sites	
1	6 (9)
2	18 (28)
3	23 (35)
4	15 (23)
5	3 (5)
Plevral Effusion	
Yes	22 (33.8)
No	43 (66.2)

ECOG: The Eastern Cooperative Oncology Group; BMI: Body Mass Index.

Survival Analysis

Progression developed in 36 (65%) patients, and 7 (11%) patients died before a response could be evaluated while undergoing nivolumab therapy. The median PFS (mPFS) was 6 months (95% CI 3.4–8.6). When using Cox regression analysis, no factor other than NLR could be identified as having an impact on PFS (p=0.015, [HR]:0.46, 95% CI:0 .23–0.91). In those with NLR ≥ 3.2 < 3.2, the mOS was 8 months and 4 months, respectively (Fig. 1).

Twenty-eight (43%) patients died during the follow-up. Median OS (mOS) was 9 (95% CI 5.2–18.1) months. In those with CLAS 0, 1, 2, 3 the mOS was 3, 7, 15, and 15 months, respectively (p=0.002). In those with NLR ≥ 3.2 < 3.2, the mOS was 7 months and 15 months, respectively. Univariate Cox regression analyses showed that high baseline NLR, low baseline albumin and CLAS < 2 (0-1) were a significant risk factors for poor OS (p=0.038, [HR]: 1.28 95% CI:1.12–1.44, p=0.03, [HR]: 0.91, 95% CI:0.84–0.99, p=0.004, [HR]: 0.287, 95% CI:0.12–0.68, respectively). But only CLAS <2 was found as independent prognostic factors for OS in multivariate analyses (p=0.013, [HR]: 0.325, 95% CI: 0.13–0.79) (Figs. 2, 3) The median overall survival times of the groups and the data of Cox analysis are summarized Table 2.

Conclusion

In the current study of 65 mNSCLC patients receiving nivolumab as monotherapy, the majority of patients were denovo metastatic (66%) and approximately half (49%) had SCC. Smoking history was present in 68% of them. In the study kohort, mPFS was 6 months (95% CI 3.4–8.6), and mOS was 9 (95% CI 5.2–18.1) months. In those with NLR ≥ 3.2 < 3.2, the mOS was 7 months and 15 months, respectively. In those with CLAS 0, 1, 2, 3, the mOS was 3, 7, 15, and

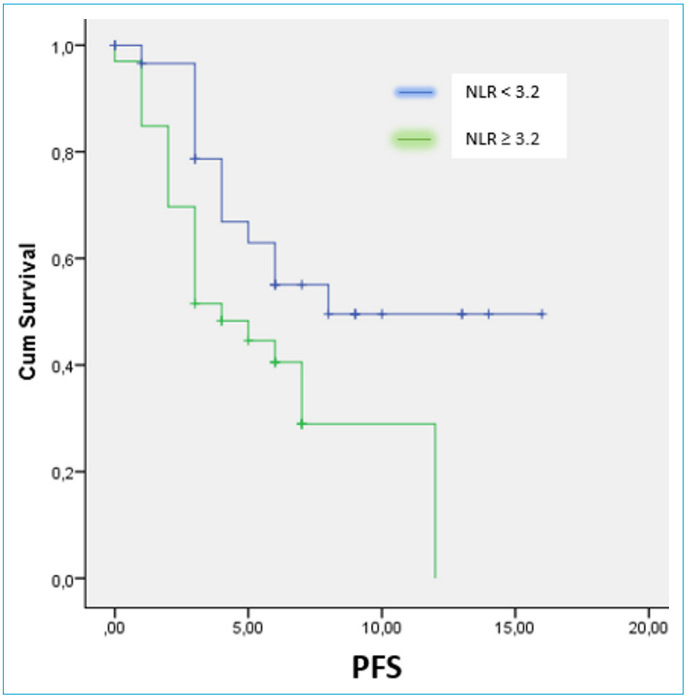

Figure 1. Progression-free survival chart according to neutrophil lymphocyte ratio.

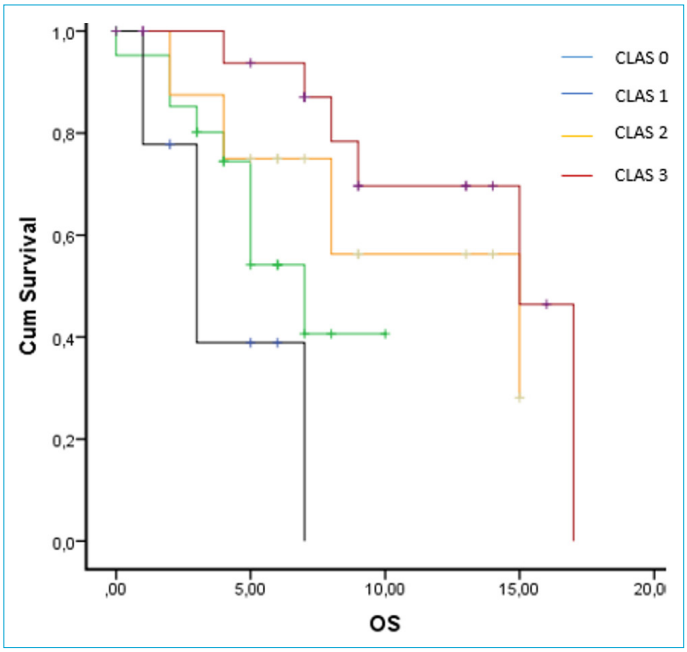

Figure 2. Overall survival chart according to the combined LDH-albumin score (CLAS) groups.

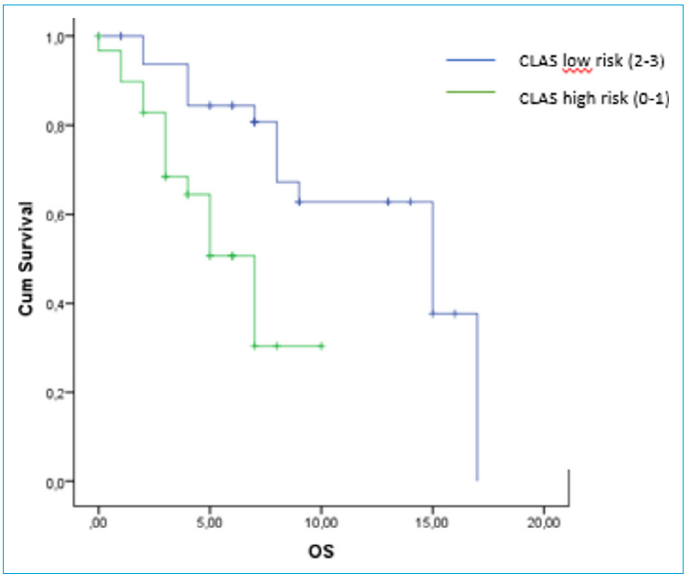

Figure 3. Overall survival chart according to high or low combined LDH-albumin score (CLAS).

15 months, respectively (p=0.002). Those with low CLAS (0-1) and those with high CLAS (2-3) had a median survival of 7 and 15 months (p=0.013). NLR was found as a predictive marker for PFS (p=0.015, [HR]:0.46, 95% CI:0 .23–0.91) and CLAS < 2 (0 and 1) was found as an independent prognostic factor for OS (p=0.013, [HR]:0.325, 95% CI:0.13–0.79).

The effect of systemic inflammatory response on carcinogenesis and metastasis has attracted attention in recent years. Inflammatory cells and tumor microenvironment have been found to cause tumor progression and metastasis. However, it was observed that the blood levels of inflammatory biomarkers were affected by various psychological, pathological and physical factors present at the time of measurement.[11] Therefore, the efficiency of using the ratios of inflammatory markers to each other was thought to be better in predicting the prognosis. For this purpose, some inflammation indices such as NLR, PLR, SII, CRP-albumin ratio (CAR), and LDH/albumin ratio (LAR) were created and they have been shown to be effective in many cancer prognosis.[12-16]

According to a pooled analysis of 17 studies investigating the efficacy of NLR in patients with advanced-stage NSCLC treated with an immune checkpoint inhibitor (ICI), pre-treatment NLR was associated with short PFS (HR = 1.44, 95% CI 1.26–1.65; p<0.001) and OS (HR = 2.86, 95% CI 2.11–3.87; p<0.001).[17] It was seen that this relationship was not valid only if the cut-off value of NLR was <3 and in Asian race. A comprehensive meta-analysis by Meghan A. et al., including many types of cancer, shows that there is an association between high NLR and poor outcomes in 92% of the studies. In this study, it was warned that smoking may be a confounder factor, especially in patients with oral and respiratory system cancers.[18] In our study, the cut-off value of NLR was found to be 3.2. But the vast majority (68%) of our cohort had a history of smoking. This may have been effective in the result that NLR was predictive for PFS ([HR]:0.46, 95% CI:0 .23–0.91, p=0.015) but not for OS (p=0.316).

In a meta-analysis evaluating the effect of PLR in lung cancer patients, it was found that high PLR was poor prognostic but it did not affect PFS.[19] In the study of Wang et al., SII was predictive for PFS and OS, but the heterogeneity of the datas was high (I^2 = 60.6%, p=0.01 for OS, I^2 = 58.2%, p=0.092 for PFS).[20] Asif et al. found that low SII increased PFS but did not affect OS.[21] In our study, the p value was not significant in ROC analysis for PFS and SII. However, median values were taken as cut-off and univariate analysis was performed, but PLR and SII did not affect either PFS or OS. This may be due to the differences in the operation, radiotheraphy, comorbidity, pharmacy and smoking history of the patients.

There are many studies showing the prognosis of LDH/albumine ratio (LAR), which is calculated using LDH and albumin values, in various cancer types. It was revealed that high LAR level before treatment negatively affects OS and PFS.[16] Zhihui et al. stated 3-year and 5-year OS rates; 90.9% and 87.1% in the low LAR group and 56% and 44% in the high LAR group, in the patients with colon cancer. Although LAR has been studied extensively, there is only one study in the literature on the predictive role of the CLAS score. In

the study by Daher et al., baseline LDH and alb levels were found to be significantly associated with survival.[10] CLAS score was created using these two variables and patients were divided into 4 groups according to low/high LDH and albumin (CLAS 0: High LDH, low albumin, CLAS 1: Low LDH, low albumin, CLAS 2: High LDH, high albumin, CLAS 3: Low LDH, high albumin). Ranking by prognosis was as follows; CLASS 0 < CLASS 1 < CLASS 2 < CLAS. It was suggested that the CLAS score would be a good prognostic factor for predicting OS.[10] The number of patients in our study was approximately twice that of this study. And in our study LDH was not a predictive marker. In the multivariate Cox regression analysis, CLAS score was found to be important risk factors for poor OS. However, there was no significant difference in survival between CLAS 2 and CLAS 3, but survival was significantly lower in those with CLAS < 2 (see table 3 and figures). This result was in agreement with previous study. In order to better see the prognostic effect of CLAS score, studies with larger number and more homogeneous patients are needed.

Median OS was found as 12 months in nonsquamous NSCLC patients (Checkmate 057) and 9 months in squamous NSCLC patients (Checkmate 017) using nivolumab in the second serial.[5,22] In our study, patients with squamous

Table 2. The median overall survival times of the groups and the data of Cox analysis

Characteristics	n (%)	Median Overall) Survival (months	Univariate analyzes HR (95% CI)	p	Multivariate analyzes HR (95% CI)	p
Body Mass Index						
< 30	30 (46)	9	1	0.829		
≥ 30	35 (54)	15	0.78 (0.60-0.91)			
ECOG PS						
0-1	57 (88)	14	1	0.378		
≥ 2	8 (12)	6	1.18 (1.04-2.37)			
Histologically subtype						
Adenocarcinoma	26 (40)	8	1	0.806		
Squamous cell	32 (49)	9	0.96 (0.58-0.99)			
PLR						
< 199	34 (52)	15	1	0.75		
≥ 199	31 (48)	8	0.88 (0.41-1.88)			
SII						
< 776	33 (61)	15	1	0.451		
≥ 776	32 (49)	8	0.75 (0.35-1.60)			
NLR						
< 3.2	33 (51)	15	1	0.015	1	
≥ 3.2	32 (49)	7	1.5 (1.14-2.95)		1.32 (0.88-3.76)	0.316
LDH						
< 220	40 (62)	15	1	0.07		
≥ 220	25 (38)	8	0.49 (0.23-1.06)			
Albumin						
< 3.4	18 (28)	5	1	0.03	1	
≥ 3.4	47 (72)	15	0.91 (0.84–0.99)		1.05 (0.67-3.15)	0.344
CLAS				(0.002)		
3	19 (29)	15	1	0.008	1	
2	16 (25)	15	1.81 (0.57-5.71)	0.001	1.82 (0.58-5.76)	0.002
1	21 (32)	7	3.78 (1.17-12.17)	0.026	3.35 (1.02-10.9)	0.46
0	9 (14)	3	8.76 (2.39-32.11)		7.63 (2.05-28.4)	0.305
CLAS						
Low risk (2-3)	35 (54)	15	1	0.004	1	
High risk (0-1)	30 (46)	7	0.287 (0.12-0.68)		0.325 (0.13-0.79)	0.013

ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: Lactate dehydrogenase; NLR: Neutrophil/ Lymphocyte ratio; PLR: Platelet/ Lymphocyte ratio; SII: Systemic immun inflammation index; CLAS: Combine LDH albumin score (CLAS 0: High LDH, low albumin; CLAS 1: Low LDH, low albumin, CLAS 2: High LDH, high albumin, CLAS 3: Low LDH, high albumin).

cell carcinoma (SCC) were in the majority. In addition, patients who received nivolumab in 3th and 4th serial and patients with had a ECOG PS > 1 were also included in the study. Accordingly, it was expected to detect an mOS close to the result in Checkmate 057.

There are some limitations regarding the current study. The first limitation was that this study was obtained from retrospective data. The second limitation was that our patient group was a relatively heterogeneous patient group. Another limitation was that blood values such as neutrophils, platelets, lymphocytes and albumin could be affected by environmental factors such as infection, inflammation, systemic disease, stres, smoking. The factor that made our study powerful was the simultaneous calculation of 4 indices in the same patient group. In addition, it was the study that studied the CLAS score with the largest number of patients in the literature.

Disclosures

Acknowledgments: I sincerely thank Dinçer Aydın, Esma Türkmen Bekmez, Ulaş Işık, and Nihal Kayır for their support throughout the research process.

Ethics Committee Approval: This study adhered to the ethical standards set by institutional and national committees, and the 1964 Declaration of Helsinki and subsequent revisions. Approval was obtained from the local non-invasive clinical research Ethics Committee (Approval Number: 2023/5/53).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances since the 2004 Classification. J Thorac Oncol. 2015;10(9):1243-1260. doi:10.1097/JTO.0000000000000630
3. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for lung cancer. J Thorac Oncol. 2016;11(1):39-51. doi:10.1016/j.jtho.2015.09.009
4. Brahmer JR, Lee JS, Ciuleanu TE, et al. Five-Year Survival Outcomes with Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. J Clin Oncol. 2023;41(6):1200-1212. doi:10.1200/JCO.22.01503
5. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-1639. doi:10.1056/nejmoa1507643
6. Kazandjian D, Suzman DL, Blumenthal G, et al. FDA Approval Summary: Nivolumab for the Treatment of Metastatic Non-Small Cell Lung Cancer With Progression On or After Platinum-Based Chemotherapy. Oncologist. 2016;21(5):634-642. doi:10.1634/theoncologist.2015-0507
7. Salciccia S, Frisenda M, Bevilacqua G, et al. Prognostic role of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with non-metastatic and metastatic prostate cancer: A meta-analysis and systematic review. Asian J Urol. 2023. [Article in Press] doi:10.1016/j.ajur.2023.01.002
8. Maloney S, Pavlakis N, Itchins M, et al. The Prognostic and Predictive Role of the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Lymphocyte-to-Monocyte Ratio (LMR) as Biomarkers in Resected Pancreatic Cancer. J Clin Med. 2023;12(5). doi:10.3390/jcm12051989
9. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. J Cancer. 2018;9(18):3295-3302. doi:10.7150/jca.25691
10. Daher S, Lawrence YR, Dudnik E, et al. Nivolumab in Non-Small Cell Lung Cancer: Real World Long-Term Survival Results and Blood-Based Efficacy Biomarkers. Front Oncol. 2021;11(July):1-9. doi:10.3389/fonc.2021.625668
11. Azab B, Bhatt VR, Phookan J, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Ann Surg Oncol. 2012;19(1):217-224. doi:10.1245/s10434-011-1814-0
12. Azuma T, Matayoshi Y, Odani K, et al. Preoperative neutrophil-lymphocyte ratio as an independent prognostic marker for patients with upper urinary tract urothelial carcinoma. Clin Genitourin Cancer. 2013;11(3):337-341. doi:10.1016/j.clgc.2013.04.003
13. Yausep OE, Agarwal R, Aulina R, et al. Prognostic value of platelet to lymphocyte ratio in predicting survival of patients with metastatic castration-resistant prostate cancer receiving abiraterone acetate: An evidence-based case report and review of literature. Clin Case Reports. 2019;7(8):1585-1590. doi:10.1002/ccr3.2288
14. Wang S, Yang X, Yu Z, et al. The Values of Systemic Immune-Inflammation Index and Neutrophil–Lymphocyte Ratio in Predicting Biochemical Recurrence in Patients With Localized Prostate Cancer After Radical Prostatectomy. Front Oncol. 2022;12(June):1-9. doi:10.3389/fonc.2022.907625
15. Bao Y, Yang J, Duan Y, Chen Y, Chen W, Sun D. The C-reactive protein to albumin ratio is an excellent prognostic predictor for gallbladder cancer. Biosci Trends. 2020;14(6):428-435. doi:10.5582/BST.2020.03326
16. Aday U, Böyük A, Akkoç H. The prognostic significance of se-

rum lactate dehydrogenase-to-albumin ratio in colorectal cancer. Ann Surg Treat Res. 2020;99(3):161-170. doi:10.4174/astr.2020.99.3.161

17. Li Y, Zhang Z, Hu Y, et al. Pretreatment Neutrophil-to-Lymphocyte Ratio (NLR) May Predict the Outcomes of Advanced Non-small-cell Lung Cancer (NSCLC) Patients Treated With Immune Checkpoint Inhibitors (ICIs). Front Oncol. 2020;10(June):1-13. doi:10.3389/fonc.2020.00654
18. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med. 2020;18:1-16.
19. Ding N, Pang Z, Shen H, Ni Y, Du J, Liu Q. The Prognostic Value of PLR in Lung Cancer, a Meta-analysis Based on Results from a Large Consecutive Cohort. Sci Rep. 2016;6(October):1-9. doi:10.1038/srep34823
20. Wang Y, Li Y, Chen P, Xu W, Wu Y, Che G. Prognostic value of the pretreatment systemic immune-inflammation index (SII) in patients with non-small cell lung cancer: a meta-analysis. Ann Transl Med. 2019;7(18):433-433. doi:10.21037/atm.2019.08.116
21. Asif S, Kesireddy M, Ganti AK, Marr A, Buddharaju LN. P60.08 Systemic Immune-Inflammatory Index (SII) as a Biomarker for Metastatic Non-Small Cell Lung Cancer. J Thorac Oncol. 2021;16(10):S1167-S1168. doi:10.1016/j.jtho.2021.08.629
22. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123-135. doi:10.1056/nejmoa1504627.