

The Effect of the Prognostic Nutritional Index on Chemoradiotherapy Response in Lung Cancer

Hacer DEMİR^a, İsmail BEYPINAR^a, Meltem BAYKARA^a

^aAfyonkarahisar Health Sciences University, Department of Medical Oncology, Afyonkarahisar, TURKEY

ABSTRACT Objective: Lung cancer (LC) is the leading cause of death due to cancer worldwide. The non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) comprise approximately 85% of the malignant lung tumors. The prognostic nutritional index (PNI), which includes serum albumin levels and circulating lymphocyte counts, can reflect both the immunological and nutritional status of the cancer patients. In this study, we tried to evaluate the relationship between PNI and the response of chemoradiation treatment in stage III lung cancer. **Material and Methods:** We retrospectively reviewed the medical records of 63 patients with stage III NSCLC or SCLC disease and had undergone concurrent chemotherapy and radiotherapy. The patient characteristics, lymphocyte-neutrophil count, levels of hemoglobin, albumin, and C-reactive protein, pathologic subtype, stage of the disease, treatment modalities, chemotherapeutic agents, and chemoradiotherapy outcome after the treatment were recorded. PNI was defined as serum albumin levels(mg/dL) x 10 + total lymphocyte count (per mm³) x 0.005. PNI and neutrophil to lymphocyte ratio (NLR) were calculated before starting any treatment. **Results:** The patients were categorized into two groups according to the PNI (<50 or ≥50), and NLR (<.3 or ≥3). While the median overall survival was 16 months in the low PNI group, it was 27 months in the high PNI group. The cut-off value of the PNI was also its median value and was determined to be 50. Despite the numerical difference in median OS between groups, according to the PNI groups, there was no statistical difference in terms of OS. No difference was observed between NLR groups categorized for cut-off levels. None of the clinical and inflammatory markers exhibited a prognostic effect on survival in multivariate analysis. **Conclusion:** In this study, we observed no relationship between inflammatory markers and prognosis in patients with stage three lung cancer who underwent chemoradiation. Although the difference was statistically insignificant, the OS was numerically higher, favoring the high PNI group.

Keywords: Lung cancer; prognostic nutritional index; neutrophil lymphocyte ratio; prognosis; chemoradiation

Globally, lung cancer (LC) is the leading cause of cancer-related death. Nearly 85% of the malignant lung tumors occur due to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).^{1,2} Although rapid advances have taken place in both lung cancer detection and treatment, and the 5-year survival rates are still inconclusive.³

Nearly one-fourth of the patients with NSCLC are diagnosed with locally advanced stage (stage III) and have a poor prognosis.⁴ For this condition, two treatment choices may be offered, induction chemotherapy followed by surgery or concurrent chemoradiation therapy.^{5,6} Nevertheless, even with advanced surgical techniques and postoperative con-

solidation chemotherapies, the local recurrence rates are 20-40%.⁷

Many prognostic factors for lung cancer, such as tumor size, lymph node involvement, gender, age, weight loss, and smoking, may affect the course of the disease.⁸ Recently several studies have reported that immunological parameters can affect the outcome.^{9,10} The systemic inflammatory response has an essential role in the development and progression of many solid tumors.¹¹ Increased neutrophil count was found to be associated with poor prognosis, and lymphocyte count is an independent prognostic factor in solid cancers.¹² Some methods to measure systemic inflammation were established, such as platelet to

Correspondence: İsmail BEYPINAR

Eskişehir City Hospital, Clinic of Medical Oncology, Eskişehir, TURKEY

E-mail: ibeypinar@yahoo.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 13 Apr 2020

Received in revised form: 06 Jul 2020

Accepted: 20 Jul 2020

Available online: 25 Aug 2020

2452-3364 / Copyright © 2020 by Turkish Society of Medical Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



lymphocyte ratio (PLR), PNI, and neutrophil to lymphocyte ratio (NLR). These parameters were found to be correlated with poor prognosis in a variety of cancers including NSCLC.¹³⁻¹⁷

Besides immunological parameters, the impact of nutritional status on prognosis in advance stage cancers is known, and high serum albumin level correlates with better survival in lung cancer.¹⁸

The prognostic nutritional index (PNI), defined for the first time by Onodera et al., is calculated by using serum albumin level and circulating lymphocyte count, which can reflect both immunological and nutritional status of the cancer patients.¹⁹

Various studies recently showed that PNI correlates with prognosis in different types of human cancers such as colorectal, lung, gastric and, esophageal cancers.^{2,20-24}

Several hypotheses tried to comprehend this relationship between prognosis and lymphocyte counts. Lymphocytes are essential parts of the immune system and are both controllers and effectors in response to tumor progression.²⁵ Low lymphocyte count correlates with decreased survival in cancer patients.²⁶⁻²⁸ In addition, the PNI reflects both the nutritional and immunological status of the patients, which may be associated with reduced survival.²⁹ Alternatively, the poor immune and nutritional course may have an association with postoperative morbidity and complications.^{30,31}

The prognostic significance of PNI in lung cancer is being explored extensively. However, to our knowledge, no study has investigated the relationship of PNI to chemoradiotherapy. Therefore, in this study, we tried to elucidate the relationship between PNI and chemoradiation in stage III lung cancer and whether it can be used as an independent prognostic factor before chemoradiotherapy.

MATERIAL METHODS

STUDY PARTICIPANTS

In the retrospective cohort study, the archive records of patients diagnosed with lung cancer at the Afyon Kocatepe University Oncology Department were analyzed between 2012 and 2018. The patients in stage

III of disease and treated with concurrent chemotherapy and radiotherapy were included in the study regardless of histology. For staging, the patients' American Joint Committee on Cancer (AJCC) 7th edition TNM was used.

The exclusion criteria were lack of adequate cancer diagnosis, platinum-based first-line chemotherapy, and lack of follow-up. Patients with hematologic malignancies, chronic inflammatory disease, clinical suspected acute infection were also excluded.

The patient characteristics, lymphocyte-neutrophil count, hemoglobin, levels of albumin, C-reactive protein, and CEA, pathologic subtype, stage of the disease, treatment modalities, chemotherapeutic agents, and chemoradiotherapy outcome after the treatment were recorded. Also, the patients' progression-free survival (PFS), and overall survival (OS) were calculated. PFS was defined as the time from diagnosis to progression or exitus, and OS was defined as the time from diagnosis to the date of exitus due to any cause or last control.

We calculated PNI using the formula, serum albumin levels (g/dL) x 10 + total lymphocyte count (per mm³) x 0.005 as suggest by Onodera et al.¹⁹ We used 50 as the cut-off value of PNI, which was also its median value.

Blood samples were taken during outpatient control before chemoradiotherapy and patient without prior blood tests was not included in the study.

Radiotherapy was delivered 1.8-2 Gy/day for five days a week with a total dose of 60-66 Gy. Concurrent chemotherapy was started on day 1 at the beginning of radiotherapy and continued every week during radiotherapy.

RADIOLOGIC EVALUATION

The radiologic response evaluations were made via computed tomography (CT). The Response Evaluate Criteria for Solid Tumors (RECIST) was used to measure disease response. Progressive disease (PD) was determined as the rise of new lesions or increase in primary tumor volume by more than a 20%; partial response (PR) was described as the decrease by at least 30% in the sum of the longest diameters of the target lesions; complete response (CR) was defined as

the disappearance of all assessable lesions; the remaining patients who did not meet the criteria of PD or PR were considered as having stable disease (SD).³²

ETHICS

The study was approved by the institutional board of Afyonkarahisar Health Sciences University, Faculty of Medicine, and carried out by the Declaration of Helsinki principles and all applicable regulations.

STATISTICAL ANALYSIS

The statistical analysis of the study data was performed with SPSS software (Statistical Package for The Social Sciences, version 22.0, SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to determine whether data conformed to a normal distribution. Descriptive data were presented as either means or median for continuous variables, frequencies, and percentages were reported for categorical variables. Pearson's X^2 test was used to assess the associations between categorical variables. OS and PFS curves were estimated by the Kaplan-Meier product-limit estimator.

RESULTS

Sixty-three patients were enrolled in the study. The mean age of the participants was 65.2 years. All of the patients were male, and 98.4% had a history of smoking. The mean duration of smoking was 49.4 pack-years. The most frequent histologic subtype was squamous cell carcinoma. The most concurrent chemotherapy protocol included carboplatin and paclitaxel. Of the patients, 61.9% have partial remission after chemoradiation. The features of the study population are summarized in Table 1. The patients were categorized according to the PNI. The cut-off value of the PNI was determined as 50 according to the median value. In terms of chemoradiotherapy responses, there were differences between PNI groups in both the general population and non-small cell cancer histology ($p=0.18$; $p=0.19$). The comparison between groups due to PNI is presented in Table 2. While there was a numerical difference in median OS between groups, no statistical difference was observed in terms of OS, according to the PNI groups ($p=0.13$) (Figure 1). Median OS of the low and high PNI groups were 16 and 27 months, respectively. After excluding

TABLE 1: The features of the study population.

TABLE 1: The features of the study population.				
Features				
Age (years)	Mean	Median		
	65.2	64.0		
Gender	Male	Female		
N (%)	63 (100%)	0 (0%)		
Smoking	Yes	No		
N (%)	62 (98.4%)	1 (1.6%)		
Histologic Subtype	SCC	ADC	SCLC	NOS
N (%)	44 (69.8%)	5 (7.9%)	10 (15.9%)	4 (6.3%)
T stage	1	2	3	4
N (%)	1 (1.6%)	9 (14.3%)	25 (39.7%)	28 (44.4%)
N stage	0	1	2	3
N (%)	1 (1.6%)	13 (20.6%)	38 (60.3%)	11 (17.6%)
Chemotherapy Protocol	Cisplatin+Etoposide	Carboplatin+Paclitaxel	Cisplatin	Unknown
N (%)	8 (12.7%)	43 (68.3%)	11 (17.5%)	1 (1.6%)
Response to CRT	N/A	PR	SD	PD
N (%)	3 (4.8%)	39 (61.9%)	15 (23.8%)	6 (9.5%)

ADC: Adenocarcinoma, SCC: Squamous Cell Carcinoma, SCLC: Small Cell Carcinoma, NOS: Not other specified, N/A: Not-available, PR: Partial Remission, SD: Stable Disease, PD: Progressive Disease.

TABLE 2: The comparison of characteristics of the patients according to prognostic nutritional index (PNI).

	PNI<50 (n:33)	PNI>50 (n:30)	p value
Age (years)	66	63	0.25
Gender (Male/Female)	33/0	30/0	N/A
Smoking history	32	30	0.33
Histology (ADC/SCC/SCLC/NOS)	1/23/5/4	4/21/5/0	0.12
T stage (1/2/3/4)	0/5/14/14	1/4/11/14	0.72
N stage (0/1/2/3)	1/8/21/3	0/5/17/8	0.23
Response to CRT (NA/PR/SD/PD)	2/21/5/5	1/18/10/1	0.19
Hemoglobin Level (g/L)	11.5	13.2	0.001
Platelet Level (µL)	268.3	282.2	0.70
C-Reactive Protein (mg/dL)	3.9	1.5	0.008
Neutrophils (10 ³ /µL)	7.9	6.7	0.67

PNI: Prognostic nutritional index, ADC: Adenocarcinoma, SCC: Squamous Cell Carcinoma, SCLC: Small Cell Carcinoma, NOS: Not other specified, N/A: Not-available, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease.

SCLC patients, there was no difference in terms of survival (p=0.24). Also, no difference was observed between groups when NLR was categorized for both cut-off levels two and three for non-small cell cancers (p=0.31; p=0.36). The chemoradiation responses were different in NLR subgroups if the cut-off value was determined as 2; otherwise, no difference was observed (p=0.012; p=0.45). The number of patients who exhibited partial response was significantly higher in the low NLR group, while the stable disease favored the high NLR group. The percentage of the patients in NLR low and high groups was 74% and 30% in PR and 19% and 46% in SD, respectively (p=0.003; p=0.04). The significant statistical difference has remained in the non-small cell group (p=0.02) (Table 3). Multivariate analysis revealed that none of the clinical and inflammatory markers had a

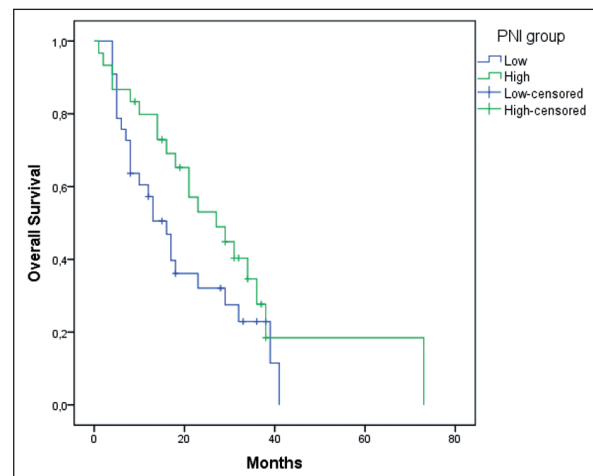


FIGURE 1: The effect of the prognostic nutritional index (PNI) on overall survival (OS) in locally advanced lung cancer.

prognostic effect on survival. The comparison of the groups in terms of PNI is presented in Table 2.

TABLE 3: The difference in chemoradiation response between groups.

Groups	PR		SD		PD		p-value
	Low	High	Low	High	Low	High	
PNI* (%)	21/31 (67)	18/29 (62)	5/31 (16)	10/29 (34)	5/31 (16)	1/29 (3)	0,10
NLR2* (%)	4/13 (30)	35/47 (74) [†]	6/13 (46)	9/47 (19) [†]	3/13 (23)	3/47 (6)	0,012
NLR3* (%)	16/28 (57)	23/32 (71)	9/28 (32)	6/32 (18)	3/28 (10)	3/32 (9)	0,45
PNI1 (%)	16/26 (61)	13/24 (54)	5/26 (19)	10/24 (41)	5/26 (19)	1/24 (4)	0,10
NLR21 (%)	3/12 (25)	26/38 (68) [†]	6/12 (50)	9/38 (23)	3/12 (25)	3/38 (7)	0,026
NLR31 (%)	12/24 (50)	17/26 (65)	9/24 (37)	6/26 (23)	3/24 (12)	3/26 (11)	0,50

PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, PNI: Prognostic Nutritional Index, NLR2: Neutrophil Lymphocyte Ratio Cut-Off Value 2, NLR3: Neutrophil Lymphocyte Ratio Cut-Off Value 3, *: General population, 1: Non-Small Cell Patient Group, [†]: Statistical significance.

DISCUSSION

In this study, we observed no relationship between inflammatory markers and prognosis in patients in stage III lung cancer who underwent chemoradiation treatment. Although the difference was statistically insignificant, the OS was numerically different between groups favoring high PNI (16 vs. 27 months). There is a close relationship between the inflammatory response, albumin, and lymphocyte levels in cancer patients.³³ Further, malnutrition and cachexia are frequently seen in patients with advanced cancer; often, hypoalbuminemia is observed as a reflection of this condition. Hypoalbuminemia not only shows nutritional status but also reflects tumor- or host-induced inflammatory response.³⁴ PNI, which has been calculated by using albumin and absolute lymphocyte count, is an important immune nutritional biomarker.

For various solid tumors, PNI can be used to determine prognosis, but, to our knowledge, its relationship with chemoradiotherapy has not been studied before. This is the first study that evaluates the relationship between chemoradiotherapy and PNI inpatient in stage III of lung cancer.³⁴⁻³⁶

The effect of the PNI on prognosis was shown in the pre-operative setting of NSCLC patients. Low levels of the PNI relate strongly to decreased survival. In this meta-analysis, the DFS also correlated with PNI. In patients who had low PNI levels had lower DFS compared with those with high PNI levels. In this study, low PNI levels seemed to correlate with a more advanced disease, which indicated that higher PNI levels had a protective effect against disease progression.³⁷ Mori et al. evaluated the PNI in patients with completely resected lung cancer and they observed that high PNI is a good independent prognostic factor for survival.³⁸ Furthermore rate of postoperative complications were higher in patients with low PNI levels, although not statistically significant.

A Turkish study evaluated the prognostic significance of NLR and PNI in NSCLC stage I to stage IV, and they found that low NLR and high PNI levels associated with better prognosis in both early-stage and metastatic patient groups.³⁹ In this study,

we used 49.5 as the cut off value for PNI. The mean OS for the low and high group patients was 7 and 33 months, respectively.

Although the treatment or the stage of the NSCLC differs, the prognostic impact of inflammatory markers is still observed. Deng et al. reported the prognostic effect of inflammatory markers in patients treated with first-generation tyrosine kinase inhibitors in advanced lung adenocarcinoma.⁴⁰ Also, in patients undergoing immunotherapy, inflammatory markers were reported as being prognostic in advanced NSCLC.⁴¹ In a different study, low PNI values correlated with inferior OS in NSCLC. These patients had lower DFS when compared with those in the high PNI group. In an another pooled analysis of this study, SCLC patients were confirmed to have lower OS associated with lower PNI.⁴² Tong et al. investigated the role of inflammatory markers in lung cancer and compared the prognostic power of neutrophil-lymphocyte ratio, PNI, and serum inflammatory index (SII) in locally advanced disease. While SII was confirmed to be a more potent prognostic factor than PNI in this study, PNI was still prognostic in a locally advanced group for patients who received concurrent chemoradiation.⁴³

CRP is an important inflammatory marker, and high levels of CRP can promote tumorigenesis and lead to poor prognosis in various cancer types.^{44,45} Fu et al. reported a negative correlation between CRP and PNI in patients with stage III and IV laryngeal cancer who underwent radiotherapy. In this study, patients with high CRP levels were observed to have worse survival rates.⁴⁶ Following these study observations, we found a negative relationship between PNI and CRP in our study, and the low PNI group had statistically significant high CRP levels.

Our study enrolled locally advanced patients who had undergone chemoradiation differently than other studies. Although PNI was reported being prognostic in other studies, a small sample size possibly prevented a significant prognostic effect in our research. Further studies investigating the prognostic impact of inflammatory markers, particularly on chemoradiation plus immunotherapy may be elucidative in this area.

LIMITATIONS

The study was designed retrospectively, which limited the quality of data. The disease intensity and tumor volume were not available, which may be related to PNI and prognosis. The study population was heterogeneous and not specific for one histologic subgroup. Also, the response of some patients to chemoradiation was not available.

CONCLUSION

In this study, we evaluated the effect of PNI on treatment response and survival in stage III lung cancer patients receiving chemoradiotherapy. Although the results of our study were not statistically significant, the low PNI group had a worse prognosis and relatively short overall survival. These findings suggest that PNI may be an independent prognostic factor, although not statistically significant when performed with a large number of patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Hacer Demir, İsmail Beypinar; **Design:** Hacer Demir; **Control/Supervision:** Meltem Baykara; **Data Collection and/or Processing:** İsmail Beypinar; **Analysis and/or Interpretation:** İsmail Beypinar; **Literature Review:** Hacer Demir; **Writing the Article:** İsmail Beypinar; **Critical Review:** Hacer Demir, Meltem Baykara; **References and Fundings:** Hacer Demir.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29. [[Crossref](#)] [[PubMed](#)]
2. Chen P, Wang C, Cheng B, et al. Plasma fibrinogen and serum albumin levels (FA score) act as a promising prognostic indicator in non-small cell lung cancer. *Onco Targets Ther.* June 2017;10:3107-3118. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
3. Zeng Q, Xue N, Dai D, et al. A nomogram based on inflammatory factors c-reactive protein and fibrinogen to predict the prognostic value in patients with resected non-small cell lung cancer. *J Cancer.* 2017;8(5):744-753. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
4. Stinchcombe TE, Zhang Y, Vokes EE, et al. Pooled analysis of individual patient data on concurrent chemoradiotherapy for stage III non-small-cell lung cancer in elderly patients compared with younger patients who participated in US National Cancer Institute Cooperative Group Studies. *J Clin Oncol.* 2017;35(25):2885-2892. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
5. Antoni D, Mornex F. Chemoradiotherapy of locally advanced nonsmall cell lung cancer: state of the art and perspectives. *Curr Opin Oncol.* 2016;28(2):104-109. [[Crossref](#)] [[PubMed](#)]
6. Pless M, Stupp R, Ris HB, et al; SAKK Lung Cancer Project Group. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet.* 2015;386(9998):1049-1056. [[Crossref](#)] [[PubMed](#)]
7. Feng W, Fu XL, Cai XW, et al. Patterns of local-regional failure in completely resected stage IIIA(N2) non-small cell lung cancer cases: implications for postoperative radiation therapy clinical target volume design. *Int J Radiat Oncol Biol Phys.* 2014;88(5):1100-1107. [[Crossref](#)] [[PubMed](#)]
8. Suzuki K, Nagai K, Yoshida J, et al. Conventional clinicopathologic prognostic factors in surgically resected nonsmall cell lung carcinoma: a comparison of prognostic factors for each pathologic TNM stage based on multivariate analyses. *Cancer.* 1999;86(10):1976-1984. [[Crossref](#)] [[PubMed](#)]
9. Paesmans M, Sculier JP, Libert P, et al. Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients. The European lung cancer working party. *J Clin Oncol.* 1995;13(5):1221-1230. [[Crossref](#)] [[PubMed](#)]
10. Teramukai S, Kitano T, Kishida Y, et al. Pre-treatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: an analysis of Japan Multinational Trial Organisation LC00-03. *Eur J Cancer.* 2009;45(11):1950-1958. [[Crossref](#)] [[PubMed](#)]
11. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (MGPS) predicts cancer survival independent of tumour site: a glasgow inflammation outcome study. *Br J Cancer.* 2011;104(4):726-734. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
12. Fogar P, Sperti C, Basso D, et al. Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. *Pancreas.* 2006;32(1):22-28. [[Crossref](#)] [[PubMed](#)]
13. Proctor MJ, Morrison DS, Talwar D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A glasgow inflammation outcome study. *Eur J Cancer.* 2011;47(17):2633-2641. [[Crossref](#)] [[PubMed](#)]
14. Cannon NA, Meyer J, Iyengar P, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. *J Thorac Oncol.* 2015;10(2):280-285. [[Crossref](#)] [[PubMed](#)]
15. Shimizu K, Okita R, Saisho S, et al. Prognostic nutritional index before adjuvant chemotherapy predicts chemotherapy compliance and survival among patients with non-small-cell lung cancer. *Ther Clin Risk Manag.* 2015;11:1555-1561. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]

16. Kinoshita A, Onoda H, Imai N, et al. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. *Br J Cancer*. 2012;107(6):988-993. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
17. Sheng J, Yang YP, Ma YX, et al. Low prognostic nutritional index correlates with worse survival in patients with advanced NSCLC following EGFR-TKIS. *PLoS One*. 2016;11(1):e0147226. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
18. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J*. December 2010;9:69. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
19. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. *Nihon Geka Gakkai Zasshi*. 1984;85(9):1001-1005. [[PubMed](#)]
20. Hirahara N, Tajima Y, Fujii Y, et al. Preoperative prognostic nutritional index predicts long-term surgical outcomes in patients with esophageal squamous cell carcinoma. *World J Surg*. 2018;42(7):2199-2208. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
21. Hong S, Zhou T, Fang W, et al. The prognostic nutritional index (PNI) predicts overall survival of small-cell lung cancer patients. *Tumour Biol*. 2015;36(5):3389-3397. [[Crossref](#)] [[PubMed](#)]
22. Nakatani M, Migita K, Matsumoto S, et al. Prognostic significance of the prognostic nutritional index in patients with recurrent esophageal squamous cell carcinoma. *Nutr Cancer*. 2018;70(3):467-473. [[Crossref](#)] [[PubMed](#)]
23. Sun K, Chen S, Xu J, Li G, He Y. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2014;140(9):1537-1549. [[Crossref](#)] [[PubMed](#)]
24. Yang Y, Gao P, Song Y, et al. The prognostic nutritional index is a predictive indicator of prognosis and postoperative complications in gastric cancer: a meta-analysis. *Eur J Surg Oncol*. 2016;42(8):1176-1182. [[Crossref](#)] [[PubMed](#)]
25. Rosenberg SA. Progress in human tumour immunology and immunotherapy. *Nature*. 2001;411(6835):380-384. [[Crossref](#)] [[PubMed](#)]
26. d'Engremont C, Vernerey D, Pointet AL, et al. Additive value of pre-operative and one-month post-operative lymphocyte count for death-risk stratification in patients with resectable pancreatic cancer: a multicentric study. *BMC Cancer*. 2016;16(1):823. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
27. Kobayashi N, Usui S, Kikuchi S, et al. Preoperative lymphocyte count is an independent prognostic factor in node-negative non-small cell lung cancer. *Lung Cancer*. 2012;75(2):223-227. [[Crossref](#)] [[PubMed](#)]
28. Saito H, Kono Y, Murakami Y, et al. Prognostic significance of pre- and postoperative lymphocyte counts in patients with gastric cancer. *Dig Surg*. 2019;36(2):137-143. [[Crossref](#)] [[PubMed](#)]
29. Chen XL, Xue L, Wang W, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. *Oncotarget*. 2015;6(38):41370-41382. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
30. Schwegler I, von Holzen A, Gutzwiller JP, Schlumpf R, Mühlebach S, Stanga Z. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. *Br J Surg*. 2010;97(1):92-97. [[Crossref](#)] [[PubMed](#)]
31. Watanabe M, Kinoshita T, Tokunaga M, Kaito A, Sugita S. Complications and their correlation with prognosis in patients undergoing total gastrectomy with splenectomy for treatment of proximal advanced gastric cancer. *Eur J Surg Oncol*. 2018;44(8):1181-1185. [[Crossref](#)] [[PubMed](#)]
32. Peng Y, Li Z, Zhang S, et al. Association of DNA base excision repair genes (OGG1, APE1 and XRCC1) polymorphisms with outcome to platinum-based chemotherapy in advanced non-small-cell lung cancer patients. *Int J Cancer*. 2014;135(11):2687-2696. [[Crossref](#)] [[PubMed](#)]
33. Feng JF, Chen QX. Significance of the prognostic nutritional index in patients with esophageal squamous cell carcinoma. *Ther Clin Risk Manag*. 2014;10:1-7. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
34. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). *Br J Cancer*. 2012;106(8):1439-1445. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
35. Nozoe T, Ninomiya M, Maeda T, Matsukuma A, Nakashima H, Ezaki T. Prognostic nutritional index: a tool to predict the biological aggressiveness of gastric carcinoma. *Surg Today*. 2010;40(5):440-443. [[Crossref](#)] [[PubMed](#)]
36. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative outcome in pancreatic cancer. *Br J Surg*. 2011;98(2):268-274. [[Crossref](#)] [[PubMed](#)]
37. Hu Y, Shen J, Liu RK, et al. Prognostic value of pretreatment prognostic nutritional index in non-small cell lung cancer: a systematic review and meta-analysis. *Int J Biol Markers*. 2018;33(4):372-378. [[Crossref](#)] [[PubMed](#)]
38. Mori S, Usami N, Fukumoto K, et al. The significance of the prognostic nutritional index in patients with completely resected non-small cell lung cancer. *PLoS One*. 2015;10(9):e0136897. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
39. Kos FT, Hocaçade C, Kos M, et al. Assessment of prognostic value of "neutrophil to lymphocyte ratio" and "prognostic nutritional index" as a systemic inflammatory marker in non-small cell lung cancer. *Asian Pac J Cancer Prev*. 2015;16(9):3997-4002. [[Crossref](#)] [[PubMed](#)]
40. Deng C, Zhang N, Wang Y, et al. High systemic immune-inflammation index predicts poor prognosis in advanced lung adenocarcinoma patients treated with EGFR-TKIS. *Medicine (Baltimore)*. 2019;98(33):e16875. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
41. Liu J, Li S, Zhang S, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. *J Clin Lab Anal*. 2019;33(8):e22964. [[Crossref](#)] [[PubMed](#)]
42. Wang Z, Wang Y, Zhang X, Zhang T. Pre-treatment prognostic nutritional index as a prognostic factor in lung cancer: review and meta-analysis. *Clin Chim Acta*. November 2018;486:303-310. [[Crossref](#)] [[PubMed](#)]
43. Tong YS, Tan J, Zhou XL, Song YQ, Song YJ. Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer. *J Transl Med*. 2017;15(1):221. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]
44. McSorley MA, Albergh AJ, Allen DS, et al. C-reactive protein concentrations and subsequent ovarian cancer risk. *Obstet Gynecol*. 2007;109(4):933-941. [[Crossref](#)] [[PubMed](#)]
45. Kemik O, Kemik AS, Begenik H, et al. The relationship among acute-phase response proteins, cytokines, and hormones in various gastrointestinal cancer types patients with cachectic. *Hum Exp Toxicol*. 2012;31(2):117-125. [[Crossref](#)] [[PubMed](#)]
46. Fu J, Yang X. The prognostic value of the c-reactive protein/prognostic nutritional index ratio in stage III and IV laryngeal cancer patients treated with radiotherapy. *Cureus*. 2019;11(5):e4648. [[Crossref](#)] [[PubMed](#)] [[PMC](#)]