

RESEARCH ARTICLE

Prognostic value of the systemic immune-inflammation index in lung cancer patients receiving immune checkpoint inhibitors: A meta-analysis

Yanhui Yang, Ji Li, Yi Wang, Lei Luo, Yi Yao, Xiaoyang Xie^{*}

Department of Thoracic Surgery, The First People's Hospital of Neijiang, Neijiang Affiliated Hospital of Chongqing Medical University, Neijiang, Sichuan, P.R. China

* 13990559066@163.com

Abstract

Purpose

To explore the association between the systemic immune-inflammation index (SII) score and prognosis in immune checkpoint inhibitor (ICI)-treated patients with lung cancer.

Methods

PubMed, EMBASE, Web of Science, and CNKI databases were searched up to August 1, 2024. Progression-free survival (PFS) and overall survival (OS) were the primary outcomes queried. Hazard ratios (HRs) and 95% confidence intervals (CIs) were combined, and subgroup analysis was based on pathological type [non-small cell lung cancer (NSCLC) vs. small-cell lung cancer (SCLC)], lines of ICIs (first-line vs. second- or further-line), and combinations of other therapies (yes vs. no).

Results

Twenty retrospective studies with 2424 participants were included. The pooled results demonstrated that an elevated SII was associated with poorer PFS (HR = 1.82, 95% CI: 1.49–2.21; $P < 0.001$) and OS (HR = 2.31, 95% CI: 1.73–3.09; $P < 0.001$) in lung cancer patients receiving ICIs. Subgroup analysis stratified by pathological type, lines of ICIs and combinations of other therapies for PFS and OS further revealed the predictive role of the SII in ICI-treated lung cancer patients.

Conclusion

Based on current evidence the SII is significantly related to prognosis and could serve as a reliable prognostic indicator in lung cancer patients receiving ICIs.

OPEN ACCESS

Citation: Yang Y, Li J, Wang Y, Luo L, Yao Y, Xie X (2024) Prognostic value of the systemic immune-inflammation index in lung cancer patients receiving immune checkpoint inhibitors: A meta-analysis. PLoS ONE 19(11): e0312605. <https://doi.org/10.1371/journal.pone.0312605>

Editor: Gayle E. Woloschak, Northwestern University Feinberg School of Medicine, UNITED STATES OF AMERICA

Received: August 5, 2024

Accepted: October 9, 2024

Published: November 1, 2024

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0312605>

Copyright: © 2024 Yang et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its [Supporting Information](#) files.

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Lung cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), is the most common malignancy and leading cause of tumor-related death worldwide [1–3]. Despite great advances in early screening and surgical techniques for lung cancer in recent decades, advanced-stage lung cancer still accounts for a significant proportion of all lung cancer cases [4–6]. Immune checkpoint inhibitors (ICIs) have become one of the most important therapies for advanced lung cancer, especially in driver-negative NSCLC patients [7, 8].

Currently, ICIs include mainly cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, anti-programmed death-1 (PD-1) inhibitors, and anti-programmed death-ligand 1 (PD-L1) inhibitors. PD-1 regulates T-cell activation by binding to PD-L1 and programmed death ligand 2 (PD-L2). PD-1-generated signaling terminates early TCR signaling by preventing the phosphorylation of key TCR signaling intermediates and reducing T-cell activation and cytokine formation. Therefore, PD-1 inhibitors can interrupt the negative regulatory signals of T cells and ultimately inhibit tumor growth [9]. Compared with standard chemotherapy, the application of PD-1/PD-L1 inhibitors has shown good efficacy in a number of clinical studies, increasing the efficacy and prognosis of patients [10]. Unfortunately, a significant proportion of patients do not benefit from ICIs, even those with a high PD-L1 tumor proportion score [11].

PD-L1 expression, tumor mutational burden (TMB), circulating tumor DNA (ctDNA), and microsatellite instability-high (MSI-H) status are common clinical biomarkers for predicting ICI efficacy [12]. However, the detection cost of these biomarkers is relatively high, and the detection process is complicated, which limits their clinical application. Thus, identifying more economical and convenient biomarkers to predict the therapeutic efficacy of ICIs in clinical practice is necessary.

Growing evidence has indicated that inflammation-, nutrition-, and immune-related peripheral blood indicators play a role in predicting tumor-related immunotherapy efficacy [13–15]. The long-term survival of patients with malignant tumors is closely associated with host inflammation and immunotrophic status [16, 17]. Inflammation is an important feature of the tumor microenvironment and is related to the poor prognosis of patients with tumors [16, 17]. Hematologic inflammatory parameters such as neutrophils, lymphocytes, and platelets can reflect the balance between tumor immunity and inflammation and have a certain predictive effect on the prognosis of patients with tumors [18, 19]. The systemic immune-inflammation index (SII), based on the above blood count parameters plus platelet count * neutrophil count / lymphocyte count, has been reported to have high prognostic value in solid cancer patients treated with ICIs [20, 21]. However, whether this could serve as a reliable prognostic indicator in ICI-treated lung cancer patients remains unclear.

Therefore, we aimed to further identify the prognostic value of the SII among ICI-treated lung cancer patients.

Materials and methods

The current meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 [22].

Literature search

The PubMed, EMBASE, Web of Science, and CNKI databases were searched from inception to August 1, 2024, for available studies. The following terms were used: PD-1, PD-L1, CTLA-4, ICI, immune checkpoint inhibitor, lung, pulmonary, cancer, tumor, carcinoma, neoplasm,

survival, prognosis, prognostic, systemic immune-inflammation index, and the SII. The specific search strategies were as follows: (PD-1 OR PD-L1 OR CTLA-4 OR ICI OR immune checkpoint inhibitor) AND (lung OR pulmonary) AND (cancer OR tumor OR carcinoma OR neoplasm) AND (survival OR prognosis OR prognostic) AND (systemic immune-inflammation index OR SII). Furthermore, MeSH terms and free texts were applied and all the references cited in the included studies were also reviewed.

Inclusion criteria

Studies that met the following criteria were included: 1) patients were diagnosed with primary lung cancer pathologically; 2) patients received ICIs with or without the combination of other antitumor therapies; 3) the SII was calculated before immunotherapy as follows: platelet count * neutrophil count / lymphocyte count; 4) patients were divided into elevated and normal-SII groups; and 5) progression-free survival (PFS) or (and) overall survival (OS) were (were) compared between the two groups, representing hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).

Exclusion criteria

Studies that met the following criteria were excluded: 1) reviews, case reports, editorials, letters, or animal trials; 2) HRs were not directly reported; 3) duplicated or overlapping data; 4) immunotherapy was applied as neoadjuvant immunotherapy; and 5) low-quality studies with a Newcastle–Ottawa Scale (NOS) score ≤ 5 [23].

Data collection

The following information was extracted: first author, publication year, country, sample size, pathological subtype, tumor stage, lines of ICIs, combination of therapy, detailed drugs of ICIs, cutoff values of the SII, endpoint, NOS score, HR, and 95% CI of PFS and OS.

Methodological quality assessment

The NOS scoring tool was used to evaluate the quality of the included studies. Studies with an NOS score ≥ 6 were included.

Two authors (Yanhui Yang and Ji Li) independently performed the literature search, selection, data collection, and methodological quality assessment, and all disagreements were resolved by team discussion.

Statistical analysis

All statistical analyses were performed using STATA (version 12.0) software. Heterogeneity between studies was assessed using I^2 statistics and the Q test. If significant heterogeneity was detected ($I^2 > 50\%$ and/or $P < 0.1$) the random effects model was applied; otherwise, the fixed effects model was used. HRs and 95% CIs were combined to evaluate the association between the SII and survival. Subgroup analysis based on pathological type (NSCLC and SCLC), lines of ICIs (first-line vs. second-line or further line), and combination of other therapies (yes vs. no) was conducted. Sensitivity analysis was conducted to detect the sources of heterogeneity and assess the stability of the overall results. Furthermore, Begg's funnel plot and Egger's test were conducted to detect publication bias, and significant publication bias was defined as $P < 0.05$ [24, 25].

Results

Literature search process

One hundred and seventy-nine records were identified from four databases, and 35 duplicated records were removed. After reviewing the titles and abstracts, 114 records were excluded. Seven studies were excluded because of insufficient data and one that contained duplicated data. Finally, 20 studies were included [26–45]. The detailed process is illustrated in Fig 1 and specific information for each record was shown in S1 Table.

Basic characteristics of the included studies

All included studies were retrospective and involved a total of 2424 patients. Most studies were conducted in China (14/20) and focused on patients with NSCLC (16/20). Moreover, most enrolled patients had advanced-stage disease (TNM III–IV or extensive stage). The SII was calculated before immunotherapy as follows: platelet count * neutrophil count / lymphocyte count in all included studies, and the cutoff values of the SII ranged from 254.02–2003.95. All studies had an NOS score ≥ 6 . Other information is presented in Table 1.

The association between the SII and PFS in ICI-treated lung cancer patients

Sixteen studies identified a predictive role for the SII in PFS, in patients with lung cancer receiving ICIs. The pooled results demonstrated that an elevated SII was associated with poorer PFS (HR = 1.82, 95% CI: 1.49–2.21; $P < 0.001$; $I^2 = 47.3\%$, $P = 0.019$) (Fig 2). Furthermore, subgroup analysis based on the pathological type (NSCLC: HR = 1.80, 95% CI: 1.45–2.23, $P < 0.001$; SCLC: HR = 1.99, 95% CI: 1.20–3.29, $P = 0.008$), line of treatment (first line: HR = 1.55, 95% CI: 1.28–1.89, $P < 0.001$; second or further line: HR = 2.52, 95% CI: 0.85–7.49, $P = 0.097$) and combination of other therapies (yes: HR = 1.49, 95% CI: 1.22–1.81, $P < 0.001$; no: HR = 2.40, 95% CI: 1.79–3.22, $P < 0.001$) yielded similar results (Table 2).

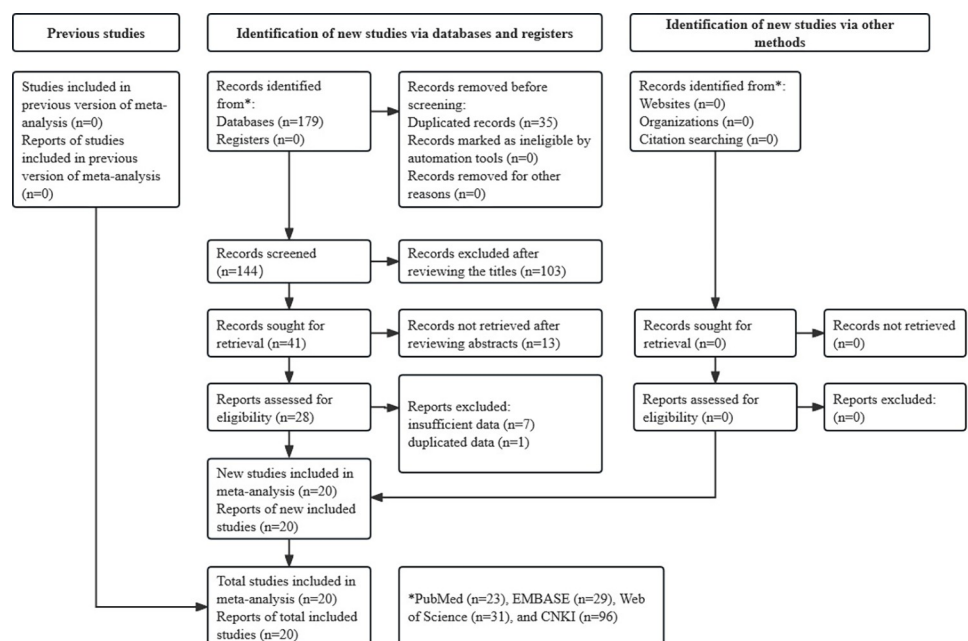


Fig 1. The flow diagram of this meta-analysis.

<https://doi.org/10.1371/journal.pone.0312605.g001>

Table 1. Basic characteristics of included studies.

Author	Year	Country	Sample size	Pathological type	Tumor stage	Lines of ICIs	Combination of therapy	Drugs of ICIs	Threshold of SII and determining method	Endpoint	NOS
Liu [26]	2019	China	44	NSCLC	TNM IV	≥2	None	Nivolumab	603.5/ROC curve	PFS, OS	6
Xiong [27]	2020	China	41	SCLC	Mixed	≥2	None	Nivolumab, pembrolizumab, atezolizumab and toripalimab	730/median value	PFS	6
Qi [28]	2021	China	53	SCLC	ES	1	Chemotherapy	Atezolizumab	533.28/ ROC curve	OS	6
Seban [29]	2021	France	51	NSCLC	TNM IIIB-IV	1	None	Pembrolizumab,	1270/X-tile software	PFS, OS	6
Wei [30]	2021	China	64	NSCLC	TNM IIIB-IV	Mixed	Mixed	Pembrolizumab	822.39/ ROC curve	PFS	6
Yang [31]	2021	China	130	NSCLC	III-IV	Mixed	Mixed	Nivolumab, pembrolizumab, sintilimab, tislelizumab and atezolizumab	1026/ ROC curve	PFS	7
Yi [32]	2021	China	121	NSCLC	TNM IIIB-IV	Mixed	None	Nivolumab, pembrolizumab, sintilimab, tislelizumab, camrelizumab, toripalimab and atezolizumab	611/ ROC curve	PFS, OS	7
Banna [33]	2022	UK	308	NSCLC	TNM IIIB-IV	1	Chemotherapy	Not reported	1444/ ROC curve	PFS, OS	7
Holtzman [34]	2022	Israel	423	NSCLC	TNM III-IIV	1	Mixed	Pembrolizumab	400/median value	OS	7
Hu [35]	2022	China	159	NSCLC	TNM III-IIV	Mixed	Mixed	PD-1 inhibitors	1369.22/ ROC curve	PFS	6
Liu [36]	2022	China	88	NSCLC	TNM IIIB-IV	1	Chemotherapy and others	Sintilimab	423/ ROC curve	OS	7
Xu [37]	2022	China	124	NSCLC	TNM IIIB-IV	Mixed	None	Nivolumab, pembrolizumab, sintilimab, tislelizumab, camrelizumab and toripalimab	1146.61/ ROC curve	PFS, OS	6
Rizzo [38]	2023	Italy	43	NSCLC	TNM IV	1	Mixed	Pembrolizumab	1235/ ROC curve	PFS, OS	8
Fang [39]	2023	China	223	NSCLC	TNM IIIB-IV	1	Chemotherapy	PD-1 inhibitors	792.07/median value	PFS, OS	6
He [40]	2023	China	58	NSCLC	TNM IV	Mixed	Chemotherapy	Carrelizumab, Sindilizumab, Tirelizumab and Atezolizumab	546.5/ ROC curve	OS	7
Baek [41]	2024	Republic of Korea	55	SCLC	ES	1	Chemotherapy	Not reported	810/ ROC curve	PFS, OS	6
Bi [42]	2024	China	178	NSCLC	TNM III-IV	Mixed	Mixed	Not reported	2003.95/ ROC curve	PFS, OS	6
Hua [43]	2024	China	68	SCLC	ES	1	Chemotherapy	Sintilimab, Durvalumab, Tislelizumab, Slunimab, Camrelizumab, Atezolizumab and Envolimab	254.02/ ROC curve	PFS, OS	6
Tang [44]	2024	China	92	NSCLC	TNM IIIB-IV	Mixed	Mixed	Pembrolizumab, nivolumab, camrelizumab, sintilimab, tislelizumab, toripalimab, penpulimab, durvalumab, atezolizumab and sugemalimab	993.7/ ROC curve	PFS, OS	6

(Continued)

Table 1. (Continued)

Author	Year	Country	Sample size	Pathological type	Tumor stage	Lines of ICIs	Combination of therapy	Drugs of ICIs	Threshold of SII and determining method	Endpoint	NOS
Yamaguchi [45]	2024	Japan	101	NSCLC	TNM III-IV	Mixed	Mixed	Nivolumab and Ipilimumab	1160.881/ ROC curve	PFS, OS	6

ICI: immune checkpoint inhibitor; SII: systemic immune-inflammation index; NOS: Newcastle-Ottawa Scale; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; TNM: tumor-node-metastasis; PD-1: programmed cell death-1; ROC: receiver operating characteristic curve; PFS: progress-free survival; OS: overall survival.

<https://doi.org/10.1371/journal.pone.0312605.t001>

The association between SII and OS in ICI-treated lung cancer patients

Sixteen studies identified a predictive role of the SII for OS. The pooled results indicated that an elevated SII was related to worse OS (HR = 2.31, 95% CI: 1.73–3.09, $P < 0.001$; $I^2 = 69.7\%$, $P < 0.001$) (Fig 3). Similarly, subgroup analysis based on pathological type (NSCLC: HR = 2.29, 95% CI: 1.67–3.13, $P < 0.001$; SCLC: HR = 2.65, 95% CI: 1.38–5.07, $P = 0.003$), line of treatment (first line: HR = 1.74, 95% CI: 1.31–2.30, $P < 0.001$; second or further line: HR = 7.69, 95% CI: 1.94–20.42, $P = 0.004$) and combination of other therapies (yes: HR = 1.83, 95% CI: 1.30–2.59, $P = 0.001$; no: HR = 4.87, 95% CI: 1.97–12.03, $P = 0.001$) produced consistent results (Table 2).

Sensitivity analysis

Sensitivity analysis for PFS and OS indicated that our results were stable and reliable and that none of the included studies showed an impact on the conclusion (Fig 4A and 4B).

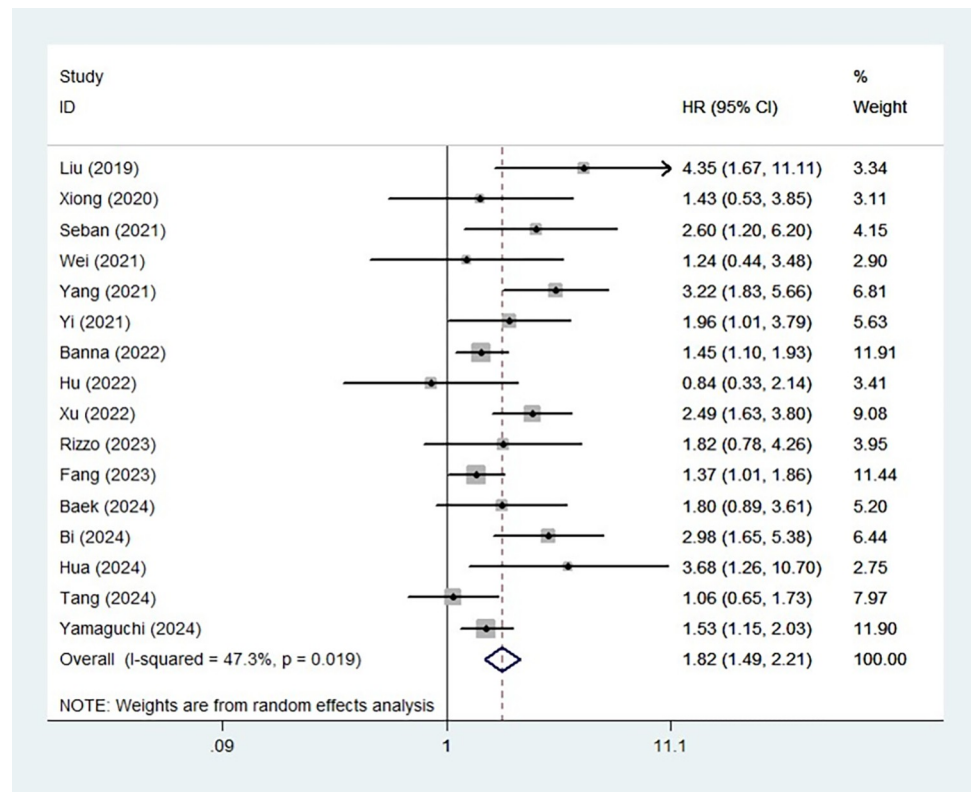


Fig 2. The association between systemic immune-inflammation index and progression-free survival.

<https://doi.org/10.1371/journal.pone.0312605.g002>

Table 2. Results of meta-analysis.

Items	No. of studies	Hazard ratio	95% confidence interval	P value	I ²	P value
Progression-free survival	16	1.82	1.49–2.21	<0.001	47.3	0.019
Pathological type						
NSCLC	13	1.80	1.45–2.23	<0.001	54.3	0.010
SCLC	3	1.99	1.20–3.29	0.008	0.0	0.412
Lines of treatment						
First line	6	1.55	1.28–1.89	<0.001	3.7	0.393
Second or further line	2	2.52	0.85–7.49	0.097	60.4	0.112
Combination of other therapies						
Yes	4	1.49	1.22–1.81	<0.001	10.4	0.341
No	5	2.40	1.79–3.22	<0.001	0	0.559
Overall survival	16	2.31	1.73–3.09	<0.001	69.7	<0.001
Pathological type						
NSCLC	13	2.29	1.67–3.13	<0.001	72.4	<0.001
SCLC	3	2.65	1.38–5.07	0.003	29.8	0.240
Lines of treatment						
First line	9	1.74	1.31–2.30	<0.001	44.2	0.064
Second or further line	1	7.69	1.94–20.42	0.004	-	-
Combination of other therapies						
Yes	7	1.83	1.30–2.59	0.001	61.6	0.016
No	4	4.87	1.97–12.03	0.001	74.2	0.009

HR: hazard ratio; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

<https://doi.org/10.1371/journal.pone.0312605.t002>

Publication bias

The Bess's funnel plots for PFS (Fig 5A) and OS (Fig 5B) were both symmetrical, with Egger's test ($P = 0.141$; $P = 0.108$) indicating nonsignificant publication bias.

Discussion

Our study demonstrates that the SII plays a role in predicting the prognosis of lung cancer patients receiving ICIs, and lung cancer patients with an elevated SII experienced a significantly worse prognosis based on current evidence. Subgroup analysis further confirmed the above findings.

In the last decade, several parameters such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) have been reported to be related to the outcomes of lung cancer patients treated with ICIs [46–50]. The SII is a novel index based on platelet, neutrophil, and lymphocyte counts. The SII is believed to have greater prognostic value than these indicators in lung cancer, as demonstrated by Liu et al. [26]. The prognostic value of the SII in lung cancer has been determined by several meta-analyses. Zhang et al. included seven studies involving 2786 patients and demonstrated that a high SII was significantly associated with poor OS among lung cancer patients (HR = 1.77, 95% CI: 1.54–2.00, $P < 0.001$), NSCLC patients (HR = 1.97, 95% CI: 1.69–2.25, $P < 0.001$), and SCLC patients (HR = 1.38, 95% CI: 1.02–1.85, $P < 0.001$) [51]. Wang et al. conducted a meta-analysis focusing on NSCLC patients and reported that pretreatment SII was associated with poor OS (HR = 1.88, 95% CI: 1.50–2.36, $P < 0.001$), disease-free survival (DFS)/PFS (HR = 2.50, 95% CI: 1.20–5.20, $P = 0.014$), and cancer-specific survival (CSS) (HR = 1.85, 95% CI: 1.19–2.92, $P = 0.007$) [52]. Moreover, they revealed that, compared with the NLR and PLR,

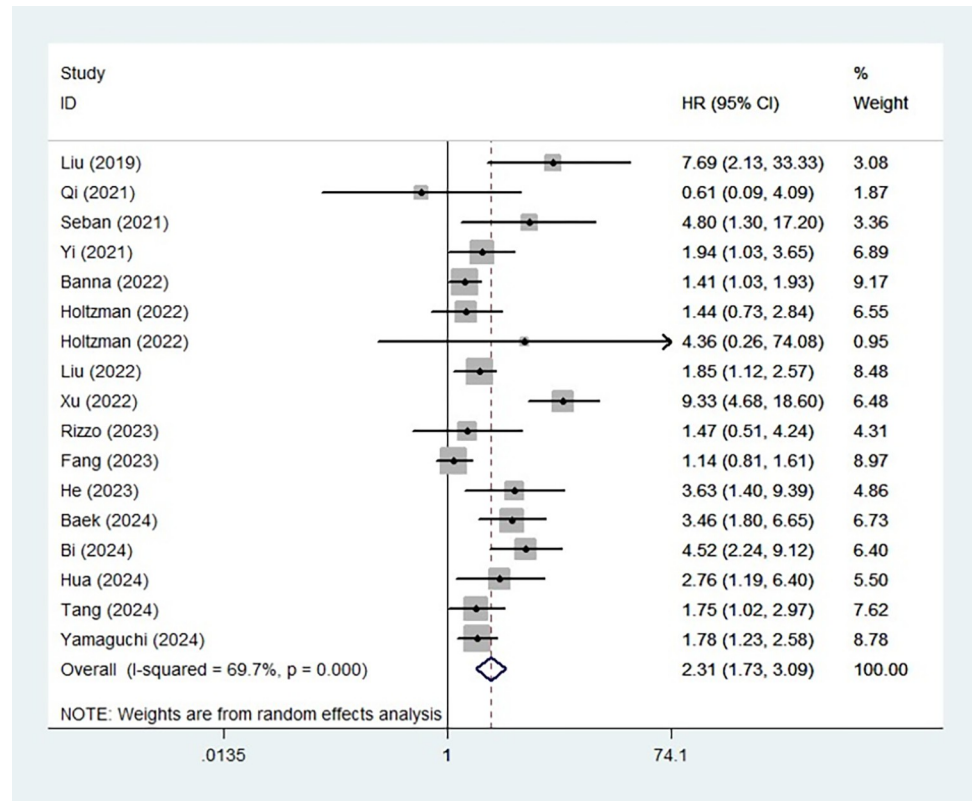


Fig 3. The association between systemic immune-inflammation index and overall survival.

<https://doi.org/10.1371/journal.pone.0312605.g003>

the SII had an obviously greater prognostic value in patients with NSCLC [52]. In 2022, a meta-analysis by Zhou et al. included eight studies focusing on SCLC and reported that an elevated SII was related to poor OS (HR = 1.52, 95% CI: 1.15–2.00, P = 0.003) but not PFS (HR = 1.38, 95% CI: 0.81–2.35, P = 0.238) [53]. However, the conclusions of these meta-analyses are relatively rare, and patients receiving ICIs constitute a special group of patients with lung cancer. More specific analyses of the prognostic role of the SII in ICI-treated patients with lung cancer are needed. Therefore, we conducted this study to further characterize the prognostic value of the SII in lung cancer patients treated with ICIs.

Although we demonstrated that the SII can predict PFS and OS in ICI-treated lung cancer patients, the clinical role of the SII in lung cancer patients receiving ICIs is worthy of further

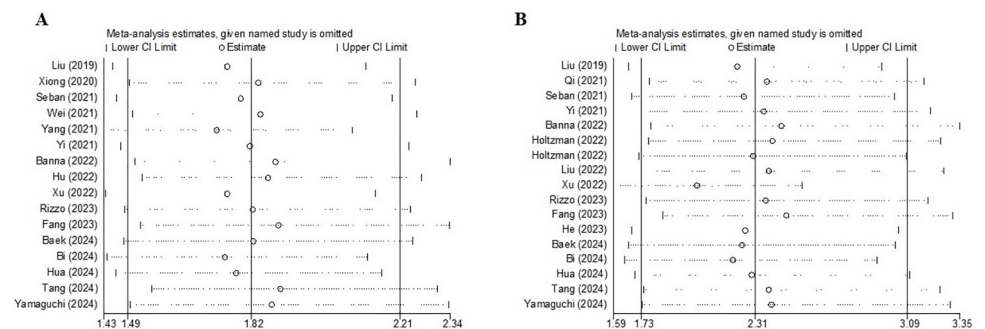


Fig 4. Sensitivity analysis for the association between systemic immune-inflammation index and progression-free survival (A) and overall survival (B).

<https://doi.org/10.1371/journal.pone.0312605.g004>

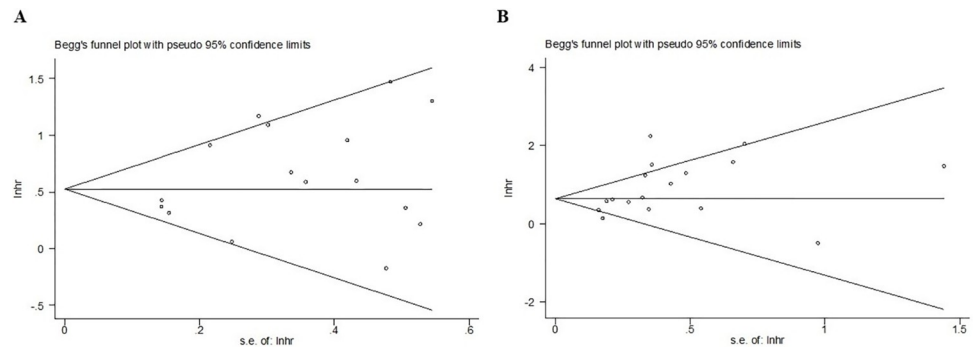


Fig 5. Begg's funnel plots for the progression-free survival (A) and overall survival (B).

<https://doi.org/10.1371/journal.pone.0312605.g005>

investigation. For example, among the included studies only three explored the association between the SII and survival of ICI-treated SCLC patients. Thus, the relationship between the SII and the prognosis of patients with SCLC receiving ICIs should be further explored. In addition, our study focused only on the SII. Some studies have revealed that the postimmunotherapy SII may also play a role in predicting long-term survival in patients with lung cancer [27, 54]. Therefore, the prognostic value of the postimmunotherapy SII and changes in the SII during immunotherapy should be further explored. Furthermore, immunotherapy is usually applied in combination with other therapies, such as chemotherapy. Therefore, it is necessary to identify the effect of the combination of other therapies on the prognostic value of the SII in ICI-treated lung cancer patients. Moreover, there are several useful indicators for predicting the efficacy of immunotherapy such as the tumor mutation burden (TMB) and the expression of PD-L1 [55–57]. Thus, a combination of the SII and these parameters might have greater prognostic value.

This meta-analysis had several limitations. First, all included studies were retrospective with relatively small sample sizes, which may have caused bias. Second, most of the included studies were conducted in China, which might affect the generalizability of our conclusions. Third, the cutoff values of the SII among the included studies varied widely and we were unable to determine the optimal cutoff value of the SII in this meta-analysis. Fourth, owing to the lack of original data we could not conduct a subgroup analysis based on other important parameters such as age, pathological subtype, sex, and ICI drugs.

Conclusion

The SII might serve as a novel and reliable prognostic indicator among lung cancer patients who receive ICIs, and patients with an elevated SII are more likely to have a worse prognosis. More prospective studies are needed to verify the above findings and explore the association between the SII and the prognosis of patients with lung cancer receiving ICIs.

Supporting information

S1 Checklist. PRISMA 2020 checklist.
(DOCX)

S1 Table. Information about 179 records from databases and reasons of their inclusion or exclusion.
(DOCX)

Author Contributions

Conceptualization: Yanhui Yang, Xiaoyang Xie.

Data curation: Yanhui Yang, Yi Yao.

Formal analysis: Yanhui Yang, Lei Luo.

Investigation: Ji Li, Lei Luo.

Methodology: Ji Li, Lei Luo.

Resources: Ji Li.

Software: Yi Wang, Yi Yao.

Supervision: Xiaoyang Xie.

Validation: Yi Wang.

Writing – original draft: Yanhui Yang, Yi Wang.

Writing – review & editing: Lei Luo, Yi Yao, Xiaoyang Xie.

References

1. Jenkins R, Walker J, Roy UB: 2022 cancer statistics: Focus on lung cancer. *Future oncology (London, England)* 2023.
2. Siegel RL, Miller KD, Wagle NS, Jemal A: Cancer statistics, 2023. *CA: a cancer journal for clinicians* 2023, 73(1):17–48. <https://doi.org/10.3322/caac.21763> PMID: 36633525
3. Zheng RS, Zhang SW, Sun KX, Chen R, Wang SM, Li L, et al.: [Cancer statistics in China, 2016]. *Zhonghua zhong liu za zhi [Chinese journal of oncology]* 2023, 45(3):212–220. <https://doi.org/10.3760/cma.j.cn112152-20220922-00647> PMID: 36944542
4. Kang MJ, Won YJ, Lee JJ, Jung KW, Kim HJ, Kong HJ, et al.: Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2019. *Cancer research and treatment* 2022, 54(2):330–344. <https://doi.org/10.4143/crt.2022.128> PMID: 35313102
5. Xia C, Dong X, Li H, Cao M, Sun D, He S, et al.: Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chinese medical journal* 2022, 135(5):584–590. <https://doi.org/10.1097/CM9.0000000000002108> PMID: 35143424
6. Ju W, Zheng R, Zhang S, Zeng H, Sun K, Wang S, et al.: Cancer statistics in Chinese older people, 2022: current burden, time trends, and comparisons with the US, Japan, and the Republic of Korea. *Science China Life sciences* 2023, 66(5):1079–1091. <https://doi.org/10.1007/s11427-022-2218-x> PMID: 36543994
7. Wang Y, Zhang Q, Miao L, Zhou Y: Nivolumab in combination with anlotinib achieved remarkable efficacy in a patient with driver-negative lung squamous cell carcinoma and PS of 4. *Annals of palliative medicine* 2020, 9(6):4384–4388. <https://doi.org/10.21037/apm-20-2096> PMID: 33302689
8. Grant MJ, Herbst RS, Goldberg SB: Selecting the optimal immunotherapy regimen in driver-negative metastatic NSCLC. *Nature reviews Clinical oncology* 2021, 18(10):625–644. <https://doi.org/10.1038/s41571-021-00520-1> PMID: 34168333
9. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al.: Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *The New England journal of medicine* 2015, 373(17):1627–1639. <https://doi.org/10.1056/NEJMoa1507643> PMID: 26412456
10. Buchbinder EI, Desai A: CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *American journal of clinical oncology* 2016, 39(1):98–106. <https://doi.org/10.1097/JCO.000000000000239> PMID: 26558876
11. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al.: Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2015, 33(18):2004–2012. <https://doi.org/10.1200/JCO.2014.58.3708> PMID: 25897158
12. Alex F, Alfredo A: Promising predictors of checkpoint inhibitor response in NSCLC. *Expert review of anticancer therapy* 2020, 20(11):931–937. <https://doi.org/10.1080/14737140.2020.1816173> PMID: 32870120

13. Mantovani A, Allavena P, Sica A, Balkwill F: Cancer-related inflammation. *Nature* 2008, 454 (7203):436–444. <https://doi.org/10.1038/nature07205> PMID: 18650914
14. Candido J, Hagemann T: Cancer-related inflammation. *Journal of clinical immunology* 2013, 33 Suppl 1:S79–84. <https://doi.org/10.1007/s10875-012-9847-0> PMID: 23225204
15. Diakos CI, Charles KA, McMillan DC, Clarke SJ: Cancer-related inflammation and treatment effectiveness. *The Lancet Oncology* 2014, 15(11):e493–503. [https://doi.org/10.1016/S1470-2045\(14\)70263-3](https://doi.org/10.1016/S1470-2045(14)70263-3) PMID: 25281468
16. Nakamura K, Smyth MJ: Targeting cancer-related inflammation in the era of immunotherapy. *Immunology and cell biology* 2017, 95(4):325–332. <https://doi.org/10.1038/icb.2016.126> PMID: 27999432
17. McFarland DC, Riba M, Grassi L: Clinical Implications of Cancer Related Inflammation and Depression: A Critical Review. *Clinical practice and epidemiology in mental health: CP & EMH* 2021, 17(1):287–294. <https://doi.org/10.2174/1745017902117010287> PMID: 35444703
18. Peng F, Hu D, Lin X, Chen G, Liang B, Li C, et al.: The monocyte to red blood cell count ratio is a strong predictor of postoperative survival in colorectal cancer patients: The Fujian prospective investigation of cancer (FIESTA) study. *J Cancer* 2017, 8(6):967–975. <https://doi.org/10.7150/jca.18000> PMID: 28529608
19. Mei Z, Shi L, Wang B, Yang J, Xiao Z, Du P, et al.: Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. *Cancer treatment reviews* 2017, 58:1–13. <https://doi.org/10.1016/j.ctrv.2017.05.005> PMID: 28602879
20. Lee JH, Hyung S, Lee J, Choi SH: Visceral adiposity and systemic inflammation in the obesity paradox in patients with unresectable or metastatic melanoma undergoing immune checkpoint inhibitor therapy: a retrospective cohort study. *J Immunother Cancer* 2022, 10(8). <https://doi.org/10.1136/jitc-2022-005226> PMID: 36002189
21. Sakai A, Iijima H, Ebisumoto K, Yamauchi M, Teramura T, Yamazaki A, et al.: Prognostic Value of Inflammatory and Nutritional Biomarkers of Immune Checkpoint Inhibitor Treatment for Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck. *Cancers* 2023, 15(7). <https://doi.org/10.3390/cancers15072021> PMID: 37046684
22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed)* 2021, 372:n71. <https://doi.org/10.1136/bmj.n71> PMID: 33782057
23. Wang Y, Li J, Chang S, Dong Y, Che G: Risk and Influencing Factors for Subsequent Primary Lung Cancer After Treatment of Breast Cancer: A Systematic Review and Two Meta-Analyses Based on Four Million Cases. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer* 2021, 16(11):1893–1908. <https://doi.org/10.1016/j.jtho.2021.07.001> PMID: 34256110
24. Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994, 50(4):1088–1101. PMID: 7786990
25. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)* 1997, 315(7109):629–634. <https://doi.org/10.1136/bmj.315.7109.629> PMID: 9310563
26. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, 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. *Journal of clinical laboratory analysis* 2019, 33(8). <https://doi.org/10.1002/jcla.22964> PMID: 31282096
27. Qi X, Ziwei H, Lingli X, Boyu Q, Xiao Z, Jing Z, et al.: Post-treatment neutrophil-to-lymphocyte ratio (NLR) predicts response to anti-PD-1/PD-L1 antibody in SCLC patients at early phase. *Cancer immunology, immunotherapy: CII* 2020, 70(prepublish).
28. Qi WX, Xiang Y, Zhao S, Chen J: Assessment of systematic inflammatory and nutritional indexes in extensive-stage small-cell lung cancer treated with first-line chemotherapy and atezolizumab. *Cancer immunology, immunotherapy: CII* 2021, 70(11):3199–3206. <https://doi.org/10.1007/s00262-021-02926-3> PMID: 33796915
29. Romain-David S, Jean-Baptiste A, Etienne G-L, Marie-Ange M, Gérald B, Christos C, et al.: Prognostic value of inflammatory response biomarkers using peripheral blood and [18F]-FDG PET/CT in advanced NSCLC patients treated with first-line chemo- or immunotherapy. *Lung Cancer* 2021, 159.
30. Wei X, Zhang C, Zang F, Chen P: Preliminary study on inflammatory markers for predicting the efficacy and prognosis of anti-PD-1 antibody treatment in patients with non-small cell lung cancer. *Chin J Clin Oncol* 2021, 48(11):547–552.
31. Yang X: The predictive role of hematological indicators in the efficacy of immune checkpoint inhibitors in patients with NSCLC. *Master. Jilin University*; 2021.

32. Yi X: Study on the efficacy and prognostic predictive value of systemic immune-inflammation index and prognostic nutrition index in patients with advanced non-small cell lung cancer treated with PD-1 inhibitors *Master*. Nanchang University; 2021.
33. Banna GL, Cantale O, Muthuramalingam S, Cave J, Comins C, Cortellini A, et al.: Efficacy outcomes and prognostic factors from real-world patients with advanced non-small-cell lung cancer treated with first-line chemoimmunotherapy: The Spinnaker retrospective study. *International Immunopharmacology* 2022, 110. <https://doi.org/10.1016/j.intimp.2022.108985> PMID: 35777264
34. Holtzman L, Moskovitz M, Urban D, Nechushtan H, Keren S, Reinhorn D, et al.: dNLR-Based Score Predicting Overall Survival Benefit for The Addition of Platinum-Based Chemotherapy to Pembrolizumab in Advanced NSCLC With PD-L1 Tumor Proportion Score ≥ 50 . *Clinical lung cancer* 2022, 23 (2):122–134.
35. Hu J: PD-L1 expression and hematological markers in the prediction of immunotherapy response and prognosis in locally advanced and metastatic non-small cell lung cancer patients. *Master*. China Medical University; 2022.
36. Liu J, Li M: Predictive value of systemic immune inflammation index in the treatment of PD-1/PD-L1 immune checkpoint inhibitors in non-small cell lung cancer. *The Journal of Practical Medicine* 2022, 38 (07):904–908.
37. Xu X: The prognostic value of peripheral blood inflammatory markers in patients with advanced non-small cell lung cancer treated with anti-PD-1 immunotherapy. *Master*. Jilin University; 2022.
38. Alessio R, Ornella C, Andrea M, Lucia G, Manuela R, Tiziana V, et al.: Assessing the role of colonic and other anatomical sites uptake by [18 F]FDG-PET/CT and immune-inflammatory peripheral blood indexes in patients with advanced non-small cell lung cancer treated with first-line immune checkpoint inhibitors. *Thoracic cancer* 2023, 14(24).
39. Fang Q, Yu J, Li W, Luo J, Deng Q, Chen B, et al.: Prognostic value of inflammatory and nutritional indexes among advanced NSCLC patients receiving PD-1 inhibitor therapy. *Clinical and Experimental Pharmacology and Physiology* 2023, 50(2):178–190. <https://doi.org/10.1111/1440-1681.13740> PMID: 36419356
40. He G, Wang J, Feng M: Predictive value of inflammatory markers of peripheral blood cells on prognosis in the advanced non-small cell lung cancer with immune therapy. *J Int Oncol* 2023, 50(06):321–327.
41. Baek JM, Cha H, Moon Y, Kim L, Kwak SM, Park ES, et al.: A Systemic Immune Inflammation Index and PD-L1 (SP142) Expression as a Potential Combined Biomarker of the Clinical Benefit of Chemo-Immunotherapy in Extensive-Stage Small-Cell Lung Cancer. *J Clin Med* 2024, 13(5). <https://doi.org/10.3390/jcm13051521> PMID: 38592329
42. Bi ZK, Xu Y, Guo L, Zhang WJ, You YT, Li JW, et al.: Effect of peripheral blood inflammatory indicators on the efficacy of immunotherapy in patients with advanced non-small cell lung cancer and chronic obstructive pulmonary disease. *Zhonghua yi xue za zhi* 2024, 104(18). <https://doi.org/10.3760/cma.j.cn112137-20231130-01247> PMID: 38742347
43. Hua Q: Predictive value of peripheral hematological indicators in first-line immunotherapy for extensive small-cell lung cancer patients. *Master*. Ganlan Medical College; 2024.
44. Tang L: Application of peripheral blood markers to predict immune-related toxicity and prognosis in patients with advanced non-small cell lung cancer. *Master*. Dalian Medical University; 2024.
45. Yamaguchi O, Kaira K, Imai H, Mouri A, Shiono A, Miura Y, et al.: Clinical Utility of Inflammatory and Nutritional Index as Therapeutic Prediction of Nivolumab plus Ipilimumab in Advanced Non-Small Cell Lung Cancer. *Oncology* 2024, 102(3):271–282. <https://doi.org/10.1159/000534169> PMID: 37725914
46. Li Y, Zhang Z, Hu Y, Yan X, Song Q, Wang G, 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). *Frontiers in oncology* 2020, 10:654. <https://doi.org/10.3389/fonc.2020.00654> PMID: 32656072
47. Liu N, Mao J, Tao P, Chi H, Jia W, Dong C: The relationship between NLR/PLR/LMR levels and survival prognosis in patients with non-small cell lung carcinoma treated with immune checkpoint inhibitors. *Medicine* 2022, 101(3):e28617. <https://doi.org/10.1097/MD.00000000000028617> PMID: 35060536
48. Chen J, Wei S, Zhao T, Zhang X, Wang Y, Zhang X: Clinical Significance of Serum Biomarkers in Stage IV Non-Small-Cell Lung Cancer Treated with PD-1 Inhibitors: LIPI Score, NLR, dNLR, LMR, and PAB. *Disease markers* 2022, 2022:7137357. <https://doi.org/10.1155/2022/7137357> PMID: 35945957
49. Matsuzawa R, Morise M, Kinoshita F, Tanaka I, Koyama J, Kimura T, et al.: Non-invasive early prediction of immune checkpoint inhibitor efficacy in non-small-cell lung cancer patients using on-treatment serum CRP and NLR. *Journal of cancer research and clinical oncology* 2022. <https://doi.org/10.1007/s00432-022-04300-x> PMID: 36006483

50. Wan L, Wu C, Luo S, Xie X: Prognostic Value of Lymphocyte-to-Monocyte Ratio (LMR) in Cancer Patients Undergoing Immune Checkpoint Inhibitors. *Disease markers* 2022, 2022:3610038. <https://doi.org/10.1155/2022/3610038> PMID: 36590752
51. Zhang Y, Chen B, Wang L, Wang R, Yang X: Systemic immune-inflammation index is a promising non-invasive marker to predict survival of lung cancer: A meta-analysis. *Medicine* 2019, 98(3):e13788. <https://doi.org/10.1097/MD.00000000000013788> PMID: 30653090
52. 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. <https://doi.org/10.21037/atm.2019.08.116> PMID: 31700869
53. Zhou Y, Dai M, Zhang Z: Prognostic Significance of the Systemic Immune-Inflammation Index (SII) in Patients With Small Cell Lung Cancer: A Meta-Analysis. *Frontiers in oncology* 2022, 12:814727. <https://doi.org/10.3389/fonc.2022.814727> PMID: 35186750
54. Suh KJ, Kim SH, Kim YJ, Kim M, Keam B, Kim TM, et al.: Post-treatment neutrophil-to-lymphocyte ratio at week 6 is prognostic in patients with advanced non-small cell lung cancers treated with anti-PD-1 antibody. *Cancer immunology, immunotherapy: CII* 2018, 67(3):459–470. <https://doi.org/10.1007/s00262-017-2092-x> PMID: 29204702
55. Killock D: TMB—a histology-agnostic predictor of the efficacy of ICIs? *Nature reviews Clinical oncology* 2020, 17(12):718.
56. Himuro H, Nakahara Y, Igarashi Y, Kouro T, Higashijima N, Matsuo N, et al.: Clinical roles of soluble PD-1 and PD-L1 in plasma of NSCLC patients treated with immune checkpoint inhibitors. *Cancer immunology, immunotherapy: CII* 2023. <https://doi.org/10.1007/s00262-023-03464-w> PMID: 37188764
57. Mariam A, Kamath S, Schveder K, McLeod HL, Rotroff DM: Biomarkers for Response to Anti-PD-1/ Anti-PD-L1 Immune Checkpoint Inhibitors: A Large Meta-Analysis. *Oncology (Williston Park, NY)* 2023, 37(5):210–219. <https://doi.org/10.46883/2023.25920995> PMID: 37216635