Predictability of Neutrophile to Lymphocyte Ratio and Platelet to Lymphocyte Ratio on the Effectiveness of Immune Checkpoint Inhibitors in Non-small Cell Lung Cancer patients: A Meta-Analysis

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Abstract

Objectives: The associations between the neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with the responses of non-small cell lung cancer (NSCLC) patients receiving immune checkpoint inhibitors (ICI) and the NLR/PLR predictive potential were evaluated via meta-analysis.

Methods: A systematic review was conducted using the PubMed, Embase, and The Cochrane Library databases until October 2021. The relationship between NLR/PLR and overall survival (OS) and progression-free survival (PFS) was evaluated using pooled hazard ratios (HR). The relationship between NLR/PLR and overall response rate (ORR) and disease control rate (DCR) was assessed via pooled odds ratios (OR). Heterogeneity between studies, publication bias, subgroup and sensitivity analyses, trim and fill meta-analysis, and the contour-enhanced funnel plot were performed using the R software.

Results: A total of 44 (out of 875) studies met the eligibility criteria, providing a sample size of 4597 patients. Patients with a high NLR were statistically significantly associated with worse outcomes, including OS (pooled HR = 2.44; $P < 0.001$), PFS (pooled HR = 2.06; $P < 0.001$), DCR (pooled OR = 0.71; $P < 0.001$), and ORR (pooled OR = 0.33; $P < 0.001$). Similarly, a high PLR was associated with poorer outcomes in response to ICI drugs, including OS (pooled HR = 2.13; $P < 0.001$) and PFS (pooled HR = 1.61; $P < 0.001$).

Conclusion: High NLR and PLR were associated with a statistically significant reduction in the efficacy of ICI drugs in NSCLC patients. Thereby, it is possible to use NLR and PLR as potential and available biomarkers in the clinical practice to predict the outcome of ICI treatment in NSCLC patients.

Keywords

effectiveness, immune checkpoint inhibitors, neutrophil-lymphocyte ratio, non-small cell lung cancer, meta-analysis, platelet-to-lymphocyte ratio

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Data Availability Statement included at the end of the article

Introduction

Lung cancer is one of the most common cancers and the leading cause of cancer death worldwide, with the total number of new cases being 2.2 million and the number of deaths being 1.8 million in 2020,[1,2] of which non-small cell lung cancer (NSCLC) accounts for about 85%.[2] The 5-year survival rate for the early stage is about 63%, and reduced to 35% for the locally advanced stage and only 7% for the metastasis stage.[2] Although surgery, radiation, and chemotherapy therapies have been significantly improved, the NSCLC survival prognosis remains low.[3] In recent years, immune checkpoint inhibitors (ICI) have significantly changed the treatment strategy of cancer in general and NSCLC in particular,[4-9] especially in advanced stages.[10,11] They are currently recommended as first-line treatment for cancer patients[12] and have become the mainstay of lung cancer treatment based on the improvement in survival.[13-15] Though improved clinical outcomes, many patients are still poorly-responded.[16] Evaluating the efficiency of drugs before prescribing them is a crucial measure to reduce medical expenses, especially in developing nations with constrained budgets. Several validated prognostic biomarkers are available, such as PD-L1, tumor mutational burden, and the Mismatch repair systems.[17-19] However, these markers had some limitations of invasive tests and the need to use histopathology or molecular genetic analysis.[17-19] Therefore, finding non-invasive, effective, and low-cost markers to predict treatment outcomes is essential for the improvement of ICI therapeutic efficacy. Some index and scores have been evaluated for their diagnostic and prognostic value in NSCLC such as systemic immune-inflammation index (SII), lung immune prognostic index (LIPI)[20] and lung immune-oncology prognostic score (LIPS).[21]

Several studies showed that two indicators namely neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) which could be easily calculated through peripheral blood counts were related to cancer drug response.[22-24] NLR and PLR dramatically increase in exitus patients and correlated to disease progression.[25] In particular, the associations between high NLR/PLR and poor treatment outcomes among NSCLC patients receiving ICI were reported in some studies with inconsistent results.[26-28] A prior meta-analysis study was conducted by N. Zhang to solve this research gap, but the study systematically searched until 01/2020 and just focused on PD-1/PD-L1 inhibitors.[29]

Hence, this comprehensive meta-analysis was conducted to assess the correlation between NLR/PLR and the effectiveness of ICIs in NSCLC patients. It also indirectly aimed to evaluate the predictive potential of these biomarkers.

Methods

Our research involved the secondary analysis of data collected from published studies and was not on human tissue/samples, so it does not need Ethics/Review board approval. This study was registered with INPLASY with the registration number INPLASY202470132. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and completed PRISMA checklist (Supplemental PRISMA checklist).

Search Strategy

A systematic search was done until October 2021 on electronic databases including PubMed, The Cochrane Library, and EMBASE using the following search terms: ('Lung cancer*' OR 'lung neoplasms*'OR 'Non-Small-Cell Lung Carcinoma*' OR 'Non Small Cell Lung Carcinoma' OR 'Non-Small Cell Lung Carcinoma' OR 'Non-Small Cell Lung Cancer' OR 'Nonsmall Cell Lung Cancer') **AND** ('Immune checkpoint inhibitor*' OR 'Immunotherapy'OR 'Immune Checkpoint Blockers' OR 'Immune Checkpoint Blockade' OR 'Immune Checkpoint Inhibition' OR 'PD-L1 Inhibitor*' OR 'PD L1 Inhibitor*' OR 'Programmed Death-Ligand 1 Inhibitor*' OR 'Programmed Death Ligand 1 Inhibitor*' OR 'CTLA-4 Inhibitor*' OR 'CTLA 4 Inhibitor*' OR 'Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitor*' OR 'Cytotoxic T Lymphocyte Associated Protein 4 Inhibitor*' OR 'PD-1 Inhibitor*' OR 'PD 1 Inhibitor*' OR 'Programmed Cell Death Protein 1 Inhibitor' OR 'Programmed Cell Death Protein 1 Inhibitors' OR 'PD-1-PD-L1 Blockade' OR 'PD 1 PD L1 Blockade' OR 'Nivolumab' OR 'Pembrolizumab' OR 'Atezolizumab' OR 'Durvalumab') **AND** ('NLR' OR 'neutrophil to lymphocyte ratio' OR 'neutrophil-to-lymphocyte ratio' OR 'neutrophil-lymphocyte ratio' OR 'PLR' OR 'platelet lymphocyte ratio' OR' platelet-to-lymphocyte ratio' OR 'platelet-lymphocyte ratio').

Inclusive and Exclusive Criteria

The studies were eligible for systematic review and meta-analysis if

- NSCLC patients in the study were treated with ICI monotherapy;
- The study explored the relationship between the pre- and/or post-treatment NLR/PLR with the ICI treatment outcomes (overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and disease control rate (DCR));
- The relevant data for meta-analysis (the hazard ratio (HR), odds ratio (OR), and 95% confidence intervals (95% CI)) were reported or could be re-calculated;
- The study design was cohort or case-control.
- If two or more studies had the same population, the study with the largest sample size and the most current information would be selected.

The studies were excluded if they were

- conference abstracts, case reports and case series, meta-analyses, or review articles;
- non-human studies;
- not written in English;
- without full text.

Data Extraction and Study Quality Assessment

All data for the systematic review (the characteristics of studies) and meta-analysis (HR, OR, 95%CI, and data used to re-calculate) were obtained. The HR values calculated based on the univariate and multivariate analysis were collected, and HR values from multivariate analysis models were preferred.

The study quality assessment was done through the Newcastle-Ottawa Scale (the NOS scale) before being included in the meta-analysis based on three criteria: selectability (maximum 4 points), comparability (maximum 2 points), and output (maximum 3 points). Based on the NOS score, the article was divided into three quality criteria: poor quality (0-2), medium quality (3-5), and good quality (6-9).[30] The studies with NOS scores over six were included in the meta-analysis.

All processes of searching, screening, data extraction, and quality assessment were independently performed by two researchers (T.N.K.V. and C.T.T.N.). Any disparity was solved by a discussion with a third party (P.T.H.).

Data Collection and Statistics

A high NLR or PLR is a value that was higher than the cut-off value in each included study. A low NLR or PLR is a value that was lower than the cut-off value in each included study.

The associations between the NLR/PLR and OS and PFS were evaluated based on pooled HR and 95%CI; those of the NLR/PLR and ORR and DCR were evaluated based on pooled OR and 95%CI.

The heterogeneity between studies was assessed using the I^2 and *P*-value of Cochran's Q test. If there was no heterogeneity ($I^2 < 50\%$ and Cochran's Q test *P*-value >0.1), the fixed effects model would be applied; otherwise, the random effects model would be used.[31,32]

If there was heterogeneity between studies, a meta-regression analysis was performed to determine the cause of the heterogeneity. The analysis included variables such as study design, geographical area, sample size, time of NLR/PLR collection (time-point), NLR/PLR cut-off values, and HR origin (the univariate and multivariate analysis), from these, subgroup analysis was performed according to the likely sources of heterogeneity.[33]

Publication bias was evaluated based on the asymmetry of the funnel plot and Egger's linear regression test.[31] If there was an asymmetric funnel, the contour-enhanced funnel plot was used to determine the cause of the asymmetric. If

publication bias was the cause, the trim and fill meta-analysis was done to identify publication bias and adjust results.[34]

The leave-one-out analysis was performed to assess the effect of a single study by omitting one study each time and re-estimating pooled results.[35]

Research using R version 4.2.3 software for analysis. A *P*-value <0.05 was considered statistically significant, except for the *P*-value of Cochran's Q test.

Results

Study Selection and Characteristics

A total of 44/875 studies that met the inclusion and exclusion criteria were collected and analyzed. The screening process and reasons for exclusion are shown in Figure 1.

The characteristics of 44 studies are summarized in Supplemental Table 1. In general, studies evaluating the associations of NLR/PLR with the effectiveness of ICI treatment have been carried out and published since 2017, with most in Asia (n = 19), followed by Europe (n = 17) and America (n = 8). The mean age of NSCLC patients ranged from 57-71 years, with a high proportion diagnosed with nonsquamous carcinoma (52%–80%). The ICI drug evaluated in most studies was nivolumab (72%), followed by pembrolizumab (34%).

Regarding study design, ten were prospective studies, and 34 were retrospective studies. The sample size was relatively small, among which 26 studies with a sample size of less than 100 (59%) and 18 studies with a sample size greater than 100 (41%).

Thirty-nine studies provided HR values in the study, and five studies needed to re-calculate HR values from the reported data.[36-39] Among eligible studies, 28 reported results relating to the NLR, 1 for the PLR,[40] and 14 reported results regarding both NLR and PLR. Concerning the time point of NLR collection, 41 studies collected the NLR pre-treatment, and seven post-treatment.[37,41-46] Regarding the PLR, 13 studies recorded the PLR pre-treatment[47] and three with post-treatment data.[42,45,46]

The Association Between the NLR and the ICI Treatment Outcomes in NSCLC Patients

There were a total of 49 studies reporting the relationship between the NLR and the ICI treatment outcomes in NSCLC patients, in which the association between NLR and OS was reported in 35 studies, PFS in 26 studies, DCR in 6 studies, and ORR in 9 studies.

The Association Between the NLR and OS. Regarding the association between NLR and OS, the meta-analysis showed that NSCLC patients with high NLR had significantly worse OS (pooled HR = 2.44; 95% CI: 2.06-2.88; *P* < 0.001) (Figure 2A) compared to those with low NLR.
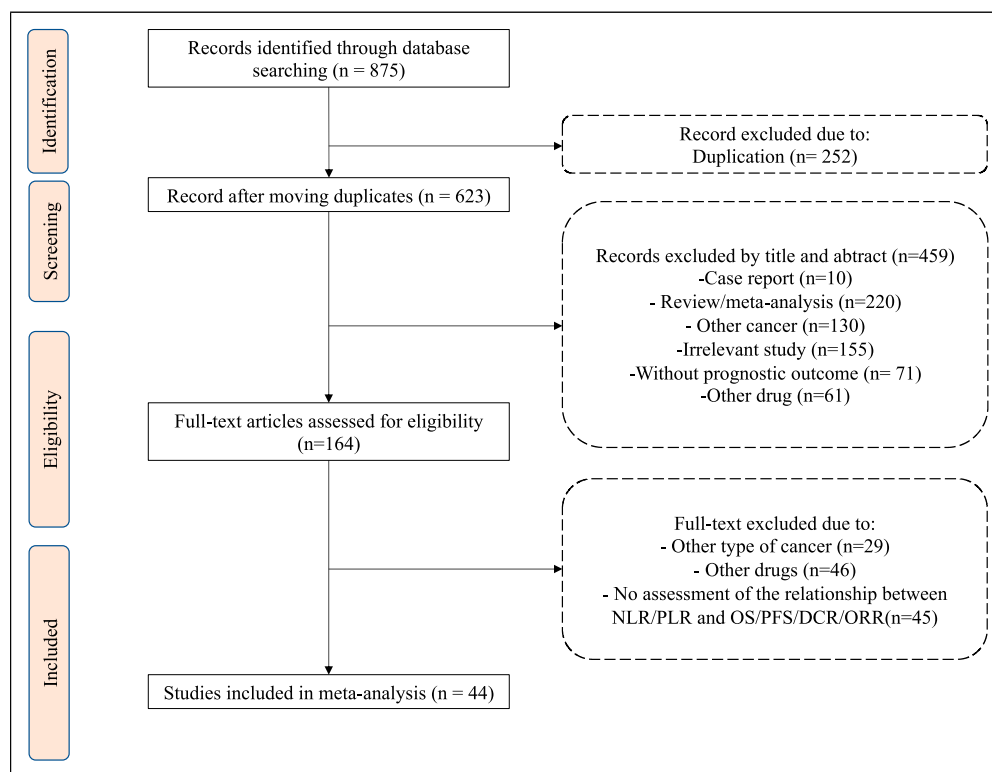
Figure 1. PRISMA flowchart.

The studies had significant heterogeneity ($I^2 = 64.0\%$; $P <$ 0.001) and had a high risk of publication bias (Figure 2B), (P-value of Egger's test <0.001). The leave-one-out sensitivity analysis demonstrated that no study affected the baseline pooled result (Figure 2C). The contour-enhanced funnel plot (Figure 2D) indicated that the studies were distributed in all three areas but mainly right-skew, so the positive publication bias might be the leading cause. The trim and fill meta-analysis performed with the assumption of no publication bias (Figure 2E) showed that HR did not change compared to the baseline pooled HR (HR = 2.07; 95%CI: 1.75-2.45). The subgroup analysis showed statistically significant associations between NLR and OS in all groups (Supplemental Table 2).

The Association Between the NLR and PFS. Considering the association between NLR and PFS, the pooled result showed that NSCLC patients with high NLR had significantly poorer PFS (pooled HR = 2.06; 95% CI: 1.72 – 2.38; $P < 0.001$) (Figure 3A). Similarly, the studies had significant heterogeneity ($I^2 = 62.2\%$; $P < 0.001$) with a high risk of publication bias (Figure 3B, P-value of Egger's test <0.001). The leave-one-out sensitivity analysis demonstrated that no study affected the baseline pooled result (Figure 3C).

The cause might be publication bias (the studies were distributed in all three areas but mainly right-skew) (Supplemental Figure 1A). The HR did not change compared to the baseline pooled HR based on the trim and fill meta-analysis (Supplemental Figure 1B). The subgroup analysis

indicated statistically significant associations in all subgroups (Supplemental Table 3).

The Association Between the NLR and DCR and ORR. The pooling analysis demonstrated that NSCLC patients with high NLR had lower DCR (OR = 0.33; 95%CI: 0.23-0.47; $P <$ 0.001) (Figure 4A), and ORR (OR = 0.71; 95%CI: 0.57 – 0.89; $P < 0.001$) (Figure 4B). There was no heterogeneity between studies ($I^2 = 0.0\%$; $P > 0.1$) and no publication bias (P-value of Egger's test >0.05). Sensitivity analysis indicated that no single study affected the results of the meta-analysis.

The Association Between the PLR and the ICI Treatment Outcomes in NSCLC Patients

A total of 23 studies assessed the relationship between PLR and the ICI treatment outcomes in NSCLC patients; in which an association between PLR and OS was reported in 13 studies, PFS in 10 studies. There was no association investigated between PLR with DCR and ORR.

The Association Between the PLR and OS. There was significant heterogeneity (I2 = 57.4%; $P = 0.004$), so the random effects model used with the pooling analysis showed that the high PLR led to significantly shorter OS (HR = 2.12; 95% CI: 1.62– 2.79; $P = 0.002$) (Figure 5A). The
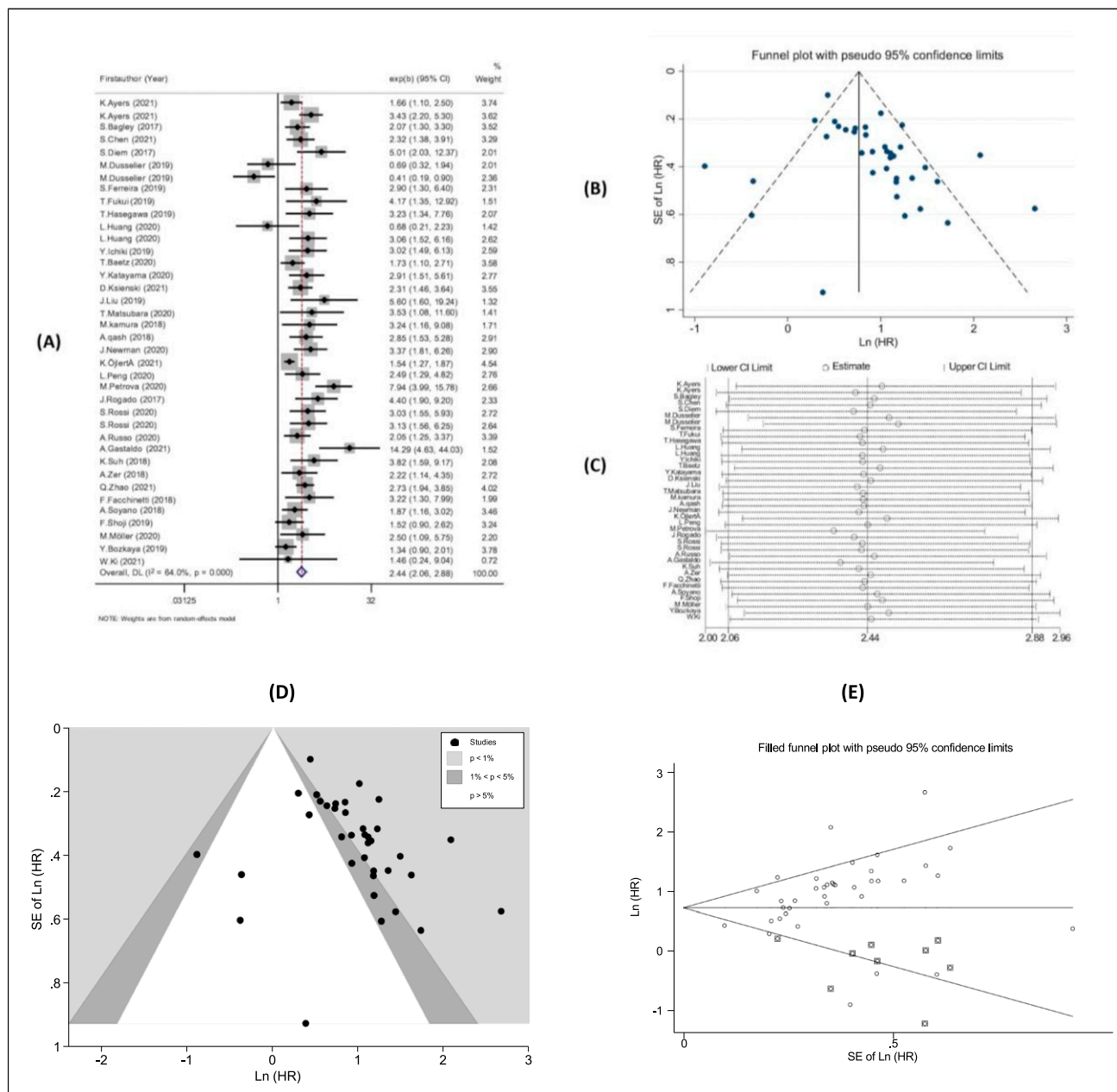
Figure 2. Meta-analysis of the association between NLR and OS, (A) the forest plot; (B) the funnel plot; (C) the sensitivity analysis; (D) the contour-enhanced funnel plot; and (E) the trim and fill meta-analysis.

symmetric funnel plots (Figure 5B) and the *P*-value of Egger's test over 0.05 indicated no publication bias. Sensitivity analysis revealed no study affected the pooled HR (Figure 5C).

The cause of publication bias (if available) might be from heterogeneity between studies (Figure 5D). The trim and fill meta-analysis assuming no publication bias, showed that HR did not change compared to the baseline pooled HR (HR = 2.12; 95%CI: 1.61-2.79) (Figure 5E).

The subgroup analysis showed statistically significant associations between PLR and OS in all subgroups, except for

one with the time-point of post-treatment (HR = 1.22; 95%CI: 0.69-2.15) (Supplemental Table 4).

The Association Between the PLR and PFS. There was no heterogeneity between ($I^2 = 8.0\%$; $P = 0.368$), so the fixed effects model used with the pooled result showed that the patients with high PLR had a risk of poorer PFS (HR = 1.61; 95% CI: 1.37 – 1.90; $P < 0.001$) (Figure 6A). The symmetrical funnel plots (Figure 6B) and the *P*-value of Egger's test over 0.05 demonstrated no publication bias between studies. Sensitivity analysis revealed that no study affected the pooled
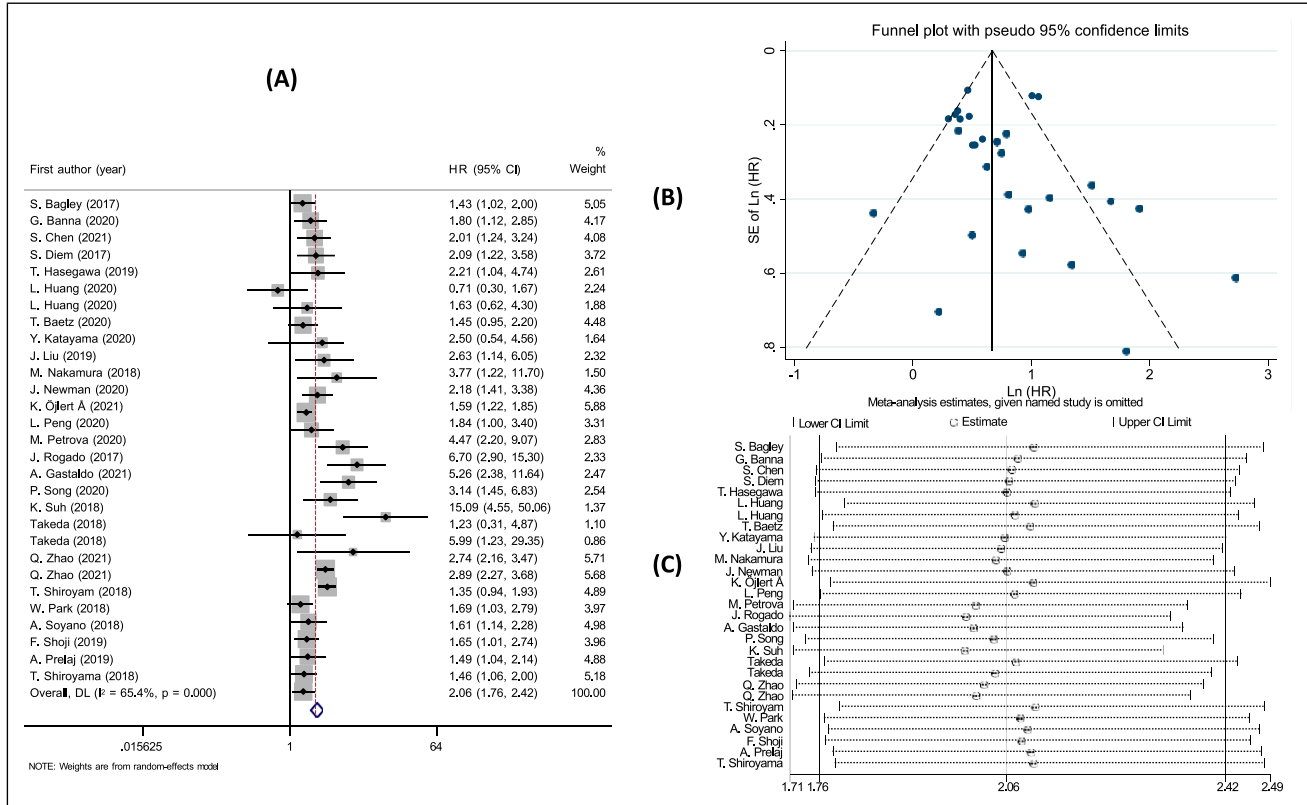
Figure 3. Meta-analysis of the association between NLR and PFS, (A) the forest plot; (B) the funnel plot; and (C) the sensitivity analysis.

Figure 4. Forest plot of the relationship between (A) NLR and DCR; (B) NLR and ORR.

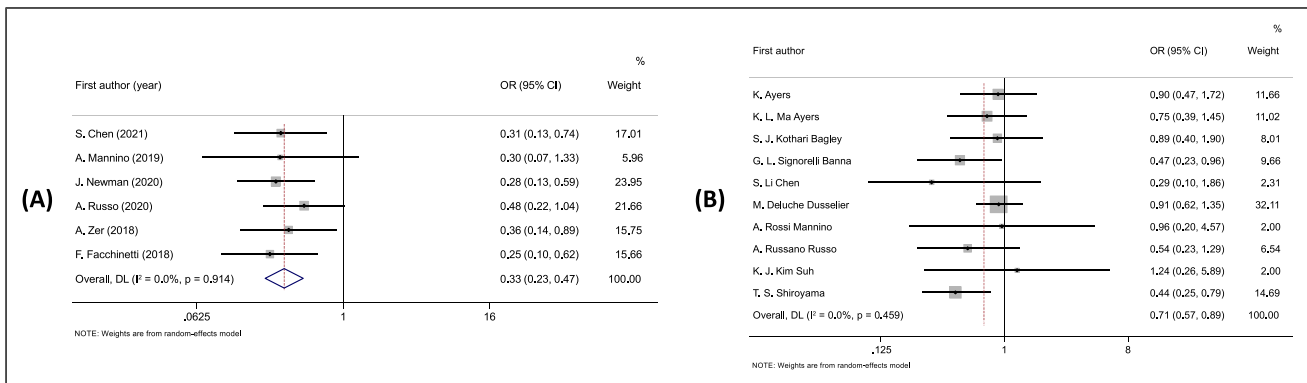result (Figure 6C). The subgroup analysis showed statistically significant associations between PLR and PFS in all subgroups, except for the time point of PLR measured in post-treatment (HR = 1.59; 95% CI: 0.93-2.74) (Supplemental Table 5).

Discussion

NLR and PLR are known as novel biomarkers based on inflammation, which have been proposed as prognostic indicators for different cancers treated with ICI.[22-24] However, the relationship between NLR/PLR and ICI treatment's effectiveness in NSCLC patients remained inconsistent. The first meta-analysis study by N. Zhang investigating the prognostic role of NLR and PLR in NSCLC treated with ICI was done in 2020 but only mentioned PD-1/PD-L1 inhibitors in 1845 NSCLC patients from 21 studies.[48] Besides, the study of N. Zhang focused on just two outcome indexes, namely OS and PFS.[48] By extending the scope of research, this study synthesized the investigation results on the NLR of
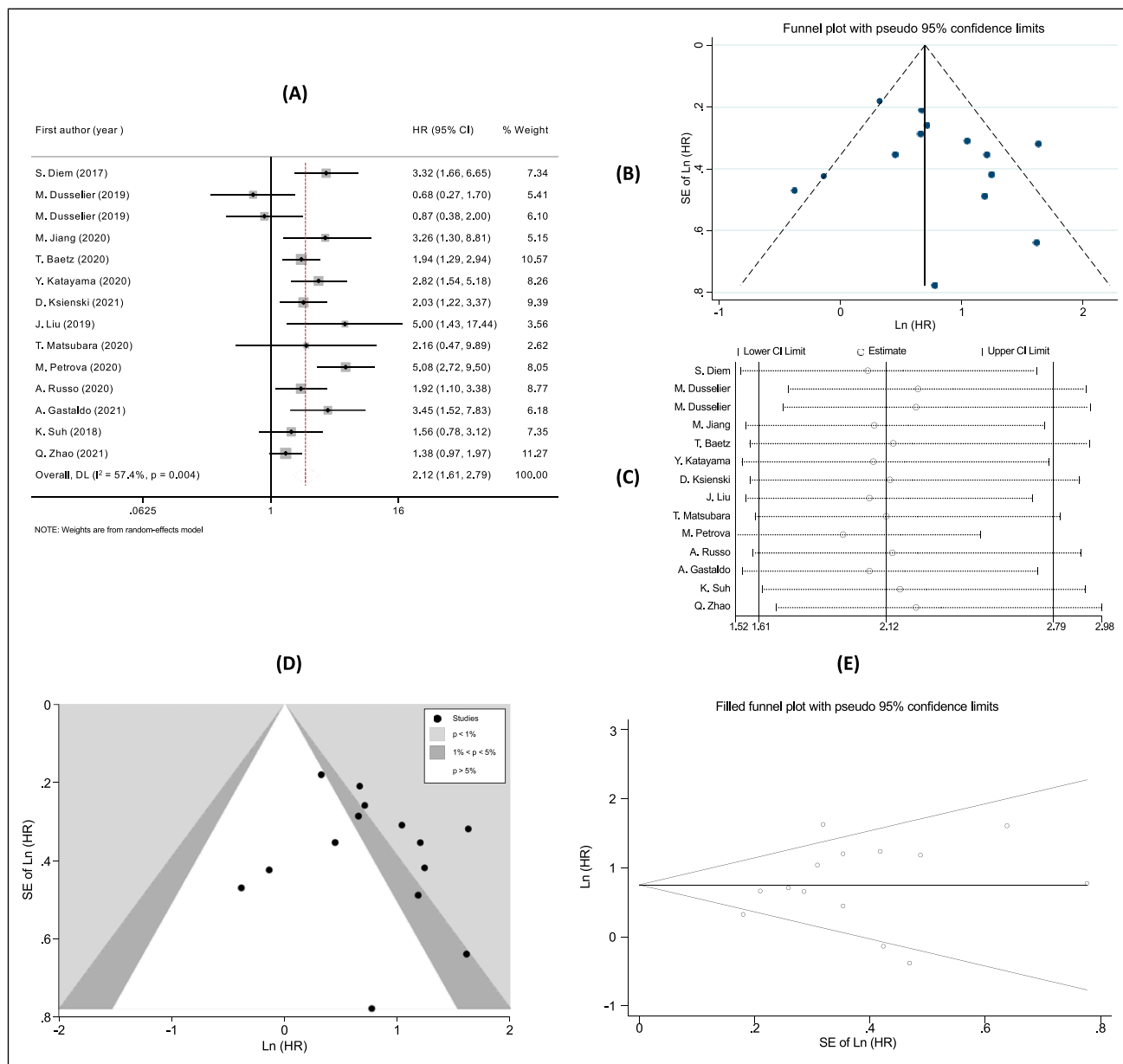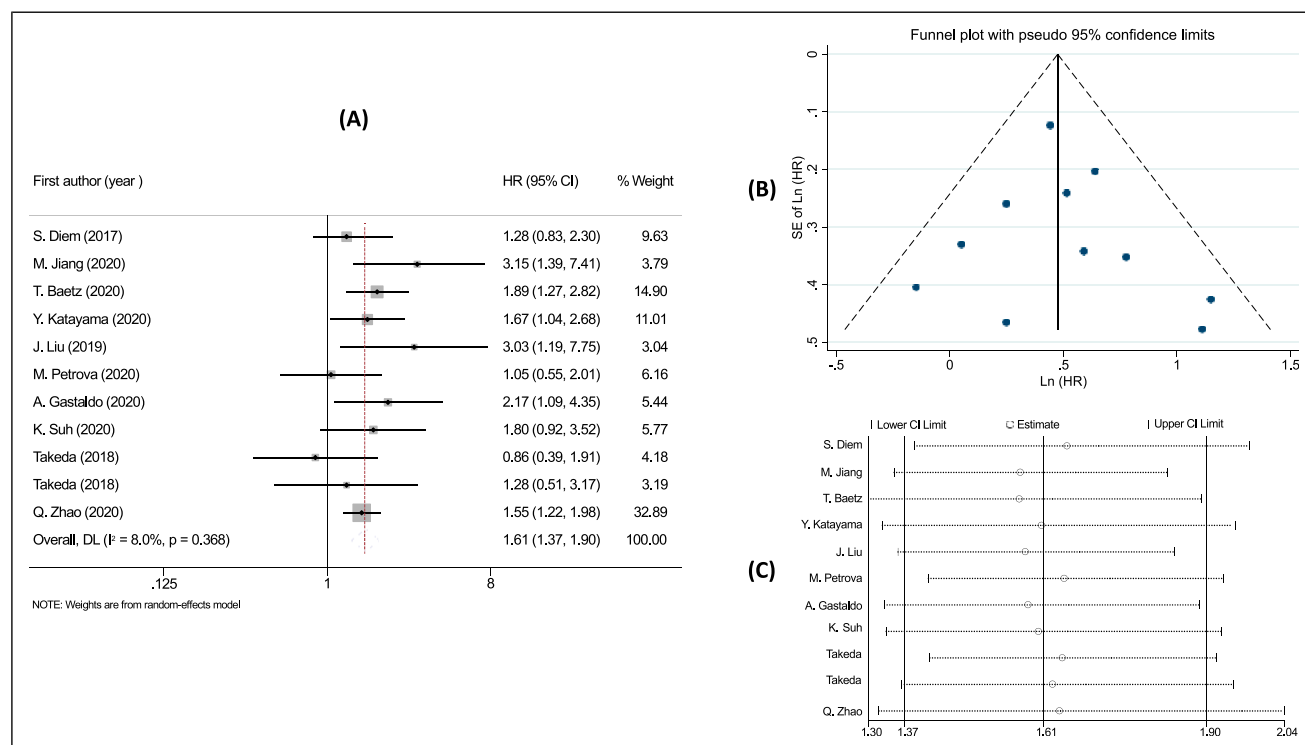
Figure 5. Meta-analysis of the association between PLR and OS, (A) the forest plot; (B) the funnel plot; (C) the sensitivity analysis; (D) the contour-enhanced funnel plot; and (E) the trim and fill meta-analysis.

4588 patients from 44 studies and that on the PLR of 1590 patients from 17 studies to analyze the relationship between NLR/PLR and ICI's effectiveness in patients. Thus, our study included numerous studies and ICI drugs in the analysis, comprising CTLA-4 and PD-1/PD-L1 inhibitors. To our knowledge, this may be the first study to comprehensively report the association between NLR/PLR and the ICI's effectiveness in treating NSCLC patients through the four outcomes (OS, PFS, ORR, and DCR).

The results of the meta-analysis showed that in the group of NSCLC patients receiving ICI drugs, high NLR related to poor treatment outcomes of ICI drugs, including a reduction in

overall survival, progression-free survival, ORR, and DCR. Although there was heterogeneity in the studies, the meta-analysis results did not change much in the subgroup analysis. The results suggested that NLR might predict the outcome of ICI therapies in NSCLC patients.

Similarly, high PLR was associated with a significant reduction in OS and PFS in ICI-treated NSCLC patients. In addition, high PLR reduced ORR by 0.47 times and DCR by 0.35 times. In subgroup analysis, high PLR post-treatment was not strongly associated with poorer OS and PFS. The associations between PLR and ORR, and DCR were still limited and may be a potential topic for further studies. Thus, the pre-

Figure 6. Meta-analysis of the association between PLR and PFS, (A) the forest plot; (B) the funnel plot; and (C) the sensitivity analysis.

treatment PLR could play a predictive role in the ICI drugs' effectiveness, thereby assisting in prescription decisions. However, due to the limited number of studies examining the connection between PLR and ORR and DCR outcomes, there is a need for additional research to establish more conclusive evidence.

There was much evidence that inflammation played an important role in affecting all steps in tumorigenesis, from tumor initiation to metastatic.[49,50] It promotes tumor growth and activates oncogenic signaling pathways,[51] leading to poorer treatment outcomes in cancer patients.[52] Specifically, NLR is a marker reflecting the balance between two forces of the immune system, namely the innate immune response, which is responsible by neutrophils, and the adaptive immunity, which is functioned by lymphocytes.[53] An increase in NLR indicates a pro-inflammatory state with relative lymphocytopenia and leukocytosis, which reduces the ability of the body to prevent the local growth of tumors and their spread.[54-56] These mechanisms indirectly suggested that patients were less likely to respond to the treatment.[57]

Similarly, high PLR was associated with increased platelet counts and decreased lymphocyte counts. Interestingly, some studies showed that platelets can be educated by cancer cells to promote the secretion of cytokines and chemokines through surface proteins, including vascular endothelial growth factor, supporting tumor growth, angiogenesis, and metastasis. In addition, platelets protected tumors from immune surveillance and inhibited the activity of natural killer cells.[58,59] Therefore,

increased platelet counts as well as PLR were associated with resistance to cancer therapies such as chemotherapy or targeted therapy in various types of cancer.[60] The response of patients to Immune Checkpoint Inhibitors (ICIs) is heavily influenced by their immune and inflammatory statuses, thus showing significant correlation with NLR and PLR.

Our study provided evidence of the relationship between NLR/PLR and the effectiveness of ICI drugs in NSCLC patients and then proposed non-invasive, highly effective, and low-cost biomarkers to predict treatment outcomes. This information is particularly beneficial for clinicians in resource-limited treatment units, where patients may have limited access to molecular biomarkers. The essential point is determining the optimal cut-off value for each marker to be used in clinical settings. As shown in our systematic review in Supplemental Table 1, the cut-off value of around 5 is chosen for most of the included studies to predict poor responders. Meanwhile, regarding PLR, there was a diversity of cut-off values among studies, ranging from 119.2 to 441.8. Therefore, our study indicates that it would be easier to monitor the dynamic change of PLR during the therapy process for prognosis thereby enabling personalized medicine.

Our study had limitations similar to the prior meta-analysis study.[48] Firstly, the large-scale studies were retrospective and had unavoidable biases. Our findings showed a significant heterogeneity between studies. However, the random-effects model, where the studies had the same influence on the pooled analysis results, was used to report the final results. In

addition, the leave-one-out and subgroup analysis were performed to calculate the actual influence of NLR/PLR on outcome indicators, and the results of these studies were consistent with the results of the previous pooled analysis. Secondly, differences in the characteristics of each study as well as differences in cut-off values of NLR, PLR, sampling time, and sampling method lead to high heterogeneity. Critical values used to define high and low NLR or PLR vary among included studies. Most studies (19/41) use an NLR cut-off of 5, but other studies employ values such as 2.8 or 6.5. Similarly, PLR cut-off values range from 144 to 400. Standardizing these critical values would enhance comparability of HR values across studies. Additionally, most of the studies collected focused on PD-1/PD-L1 checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab et al) so the relationship of NLR/PLR with the treatment outcome of NLR/PLR Other ICI drugs need to be further revealed.

Conclusion

Our study showed that high NLR/PLR were associated with a statistically significant reduction in the efficacy of ICI drugs in NSCLC patients. Thereby, it is possible to use NLR and PLR as potential and available biomarkers in clinical practice to predict the outcome of ICI treatment for NSCLC patients.

Author Contributions

All authors contributed to the study's design and revised the manuscript; P.T.H supervised the study and revised the manuscript; T.N.K.V and C.T.T.N performed the data extraction and the statistical analysis, and drafted the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Statement

Ethical Approval

This manuscript is a systematic review and meta-analysis study and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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Data Availability Statement

Supplemental Material

Supplemental material for this article is available online.

References

1. American Society of Clinical Oncology (ASCO). Lung cancer - non-small cell: statistics.
2. 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 A Cancer J Clin*. 2021;71(3): 209-249. doi:10.3322/caac.21660
3. El-Osta H, Shahid K, Mills GM, Peddi P. Immune checkpoint inhibitors: the new frontier in non-small-cell lung cancer treatment. *OncoTargets Ther*. 2016;9:5101-5116. doi:10.2147/OTT.S111209
4. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50. *J Clin Oncol*. 2021;39(21):2339-2349. doi:10.1200/JCO.21.00174
5. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383(14):1328-1339. doi:10.1056/NEJMoa1917346
6. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with Durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350. doi:10.1056/NEJMoa1809697
7. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823-1833. doi:10.1056/NEJMoa1606774
8. Socinski MA, Nishio M, Jotte RM, et al. IMpower150 final overall survival analyses for atezolizumab plus Bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. *J Thorac Oncol*. 2021;16(11):1909-1924. doi:10.1016/j.jtho.2021.07.009
9. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019; 20(7):924-937. doi:10.1016/S1470-2045(19)30167-6
10. Assi HI, Kamphorst AO, Moukalled NM, Ramalingam SS. Immune checkpoint inhibitors in advanced non-small cell lung cancer. *Cancer*. 2018;124(2):248-261. doi:10.1002/cncr.31105
11. Reck M, Rabe KF. Precision diagnosis and treatment for advanced non-small-cell lung cancer. *N Engl J Med*. 2017;377(9): 849-861. doi:10.1056/NEJMra1703413
12. Tang S, Qin C, Hu H, et al. Immune checkpoint inhibitors in non-small cell lung cancer: progress, challenges, and prospects. *Cells*. 2022;11(3):320. doi:10.3390/cells11030320

13. Reck M, Rodríguez–Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non–small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37(7):537-546.

14. Mok TS, Wu Y-L, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830.

15. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-2301.

16. Hopkins AM, Rowland A, Kichenadasse G, et al. Predicting response and toxicity to immune checkpoint inhibitors using routinely available blood and clinical markers. *Br J Cancer*. 2017;117(7):913-920. doi:10.1038/bjc.2017.274

17. Meng X, Huang Z, Teng F, Xing L, Yu J. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. *Cancer Treat Rev*. 2015;41(10):868-876. doi:10.1016/j.ctrv.2015.11.001

18. Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. *Nat Rev Cancer*. 2016;16(5):275-287. doi:10.1038/nrc.2016.36

19. Gnjatic S, Bronte V, Brunet LR, et al. Identifying baseline immune-related biomarkers to predict clinical outcome of immunotherapy. *J Immunother Cancer*. 2017;5:44. doi:10.1186/s40425-017-0243-4

20. Huang L, Han H, Zhou L, et al. Evaluation of the lung immune prognostic index in non-small cell lung cancer patients treated with systemic therapy: a retrospective study and meta-analysis. *Front Oncol*. 2021;11:670230. doi:10.3389/fonc.2021.670230

21. Mahiat C, Bihin B, Duplaquet F, et al. Systemic inflammation/nutritional status scores are prognostic but not predictive in metastatic non-small-cell lung cancer treated with first-line immune checkpoint inhibitors. *Int J Mol Sci*. 2023;24(4):3618. doi:10.3390/ijms24043618

22. Bagley SJ, Kothari S, Aggarwal C, et al. Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2017;106:1-7. doi:10.1016/j.lungcan.2017.01.013

23. Bowen RC, Little NAB, Harmer JR, et al. Neutrophil-to-lymphocyte ratio as prognostic indicator in gastrointestinal cancers: a systematic review and meta-analysis. *Oncotarget*. 2017;8(19):32171-32189.

24. Williams KA, Labidi-Galy SI, Terry KL, et al. Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. *Gynecol Oncol*. 2014;132(3):542-550. doi:10.1016/j.ygyno.2014.01.026

25. Erciyestepe M, Selvi O, Dinç Sonuşen Ş, et al. Prognostic value of inflammation and Nutrition-based scores in non-small cell lung cancer. *Med Princ Pract*. 2024;33(2):122-132. doi:10.1159/000535781

26. Huang Y, Shen A. The prediction potential of neutrophil-to-lymphocyte ratio for the therapeutic outcomes of programmed death receptor-1/programmed death ligand 1 inhibitors in non-small cell lung cancer patients: a meta-analysis. *Medicine (Baltim)*. 2020;99(34):e21718. doi:10.1097/md.0000000000021718

27. Jiang T, Qiao M, Zhao C, et al. Pretreatment neutrophil-to-lymphocyte ratio is associated with outcome of advanced-stage cancer patients treated with immunotherapy: a meta-analysis. *Cancer Immunol Immunother*. 2018;67(5):713-727. doi:10.1007/s00262-018-2126-z

28. Jiang T, Bai Y, Zhou F, et al. Clinical value of neutrophil-to-lymphocyte ratio in patients with non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors. *Lung Cancer*. 2019;130:76-83. doi:10.1016/j.lungcan.2019.02.009

29. Hasegawa T, Yanagitani N, Utsumi H, et al. Association of high neutrophil-to-lymphocyte ratio with poor outcomes of pembrolizumab therapy in high-PD-L1-expressing non-small cell lung cancer. *Anticancer Res*. 2019;39(12):6851-6857.

30. McPheeters ML, Kripalani S, Peterson NB, et al. *Closing the Quality Gap: Revisiting the State of the Science (Vol. 3: Quality Improvement Interventions to Address Health Disparities)*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012.

31. Leandro G. *Meta-analysis in Medical Research - the Handbook Forr the Understanding and Practice of Meta Analysis*. Hoboken, NJ: Blackwell Publishing Ltd; 2005.

32. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods*. 2006;11(2):193-206. doi:10.1037/1082-989x.11.2.193

33. Michael Borenstein LVH, Higgins JPT, Rothstein HR. Meta-regression. *Introduction to Meta-Analysis*. 2009:187-203.

34. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463. doi:10.1111/j.0006-341x.2000.00455.x

35. Michael Borenstein LVH, Higgins JPT, Rothstein HR. Reporting the results of a meta-analysis. *Introduction to Meta-Analysis*. 2009:365-370.

36. Ferreira S, Esteves S, Almodovar MTAS. Prognostic biomarkers in lung cancer patients treated with immunotherapy. *Ann Oncol*. 2019;30:xi6. doi:10.1093/annonc/mdz447.019

37. Rossi S, Toschi L, Finocchiaro G, Santoro A. Neutrophil and lymphocyte blood count as potential predictive indicators of nivolumab efficacy in metastatic non-small-cell lung cancer. *Immunotherapy*. 2020;12(10):715-724. doi:10.2217/imt-2019-0154

38. Russo A, Russano M, Franchina T, et al. Neutrophil-to-Lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and outcomes with nivolumab in pretreated non-small cell lung cancer (NSCLC): a large retrospective multicenter study. *Adv Ther*. 2020;37(3):1145-1155. doi:10.1007/s12325-020-01229-w

39. Sanchez-Gastaldo A, Munoz-Fuentes MA, Molina-Pinelo S, Alonso-Garcia M, Boyero L, Bernabe-Caro R. Correlation of peripheral blood biomarkers with clinical outcomes in NSCLC

patients with high PD-L1 expression treated with pembrolizumab. *Transl Lung Cancer Res*. 2021;10(6):2509-2522.

40. Jiang M, Peng W, Pu X, et al. Peripheral blood biomarkers associated with outcome in non-small cell lung cancer patients treated with nivolumab and Durvalumab monotherapy. *Front Oncol*. 2020;10:913. doi:10.3389/fonc.2020.00913

41. Ayers KL, Ma M, Debussche G, et al. A composite biomarker of neutrophil-lymphocyte ratio and hemoglobin level correlates with clinical response to PD-1 and PD-L1 inhibitors in advanced non-small cell lung cancers. *BMC Cancer*. 2021;21(1):441. doi:10.1186/s12885-021-08194-9

42. Dusselier M, Deluche E, Delacourt N, et al. Neutrophil-to-lymphocyte ratio evolution is an independent predictor of early progression of second-line nivolumab-treated patients with advanced non-small-cell lung cancers. *PLoS One*. 2019;14(7):e0219060. doi:10.1371/journal.pone.0219060

43. Huang L, Li L, Zhou Y, et al. Clinical characteristics correlate with outcomes of immunotherapy in advanced non-small cell lung cancer. *J Cancer*. 2020;11(24):7137-7145. doi:10.7150/jca.49213

44. Nakamura M, Sugihara K, Xu C, et al. NLR and its relative change early during nivolumab treatment could be useful to predict outcome in advanced NSCLC. *Ann Oncol*. 2018;29:vii80. doi:10.1093/annonc/mdy375.068

45. Suh KJ, Kim SH, Kim YJ, 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 Immunol Immunother*. 2018;67(3):459-470. doi:10.1007/s00262-017-2092-x

46. Takeda T, Takeuchi M, Saitoh M, Takeda S. Neutrophil-to-lymphocyte ratio after four weeks of nivolumab administration as a predictive marker in patients with pretreated non-small-cell lung cancer. *Thorac Cancer*. 2018;9(10):1291-1299. doi:10.1111/1759-7714.12838

47. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer*. 2017;111:176-181. doi:10.1016/j.lungcan.2017.07.024

48. Zhang N, Jiang J, Tang S, Sun G. Predictive value of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in non-small cell lung cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Int Immunopharm*. 2020;85:106677. doi:10.1016/j.intimp.2020.106677

49. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15(11):e493-503. doi:10.1016/s1470-2045(14)70263-3

50. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. *Ann Afr Med*. 2019;18(3):121-126. doi:10.4103/aam.aam_56_18

51. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646-674. doi:10.1016/j.cell.2011.02.013

52. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev*. 2013;39(5):534-540. doi:10.1016/j.ctrv.2012.08.003

53. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an Emerging marker of the relationships between the immune system and diseases. *Int J Mol Sci*. 2022;23(7):3636. doi:10.3390/ijms23073636

54. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-444. doi:10.1038/nature07205

55. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. *Br J Cancer*. 2011;105(1):93-103. doi:10.1038/bjc.2011.189

56. Wang Y, Hu X, Xu W, Wang H, Huang Y, Che G. Prognostic value of a novel scoring system using inflammatory response biomarkers in non-small cell lung cancer: a retrospective study. *Thorac Cancer*. 2019;10(6):1402-1411. doi:10.1111/1759-7714.13085

57. Mountain CF. The new International staging system for lung cancer. *Surg Clin*. 1987;67(5):925-935. doi:10.1016/s0039-6109(16)44330-6

58. Li N. Platelets in cancer metastasis: to help the "villain" to do evil. *Int J Cancer*. 2016;138(9):2078-2087. doi:10.1002/ijc.29847

59. Numico G, Russi E, Merlano M. Best supportive care in non-small cell lung cancer: is there a role for radiotherapy and chemotherapy? *Lung Cancer*. 2001;32(3):213-226. doi:10.1016/s0169-5002(00)00222-1

60. Huong PT, Nguyen LT, Nguyen XB, Lee SK, Bach DH. The role of platelets in the tumor-Microenvironment and the drug resistance of cancer cells. *Cancers*. 2019;11(2):240. doi:10.3390/cancers11020240