INPLASY

Predictability of NLR and PLR on the effectiveness of immune checkpoint inhibitors in non-small cell lung cancer patients: A Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 July 2024 and was last updated on 31 July 2024.

INTRODUCTION

Review question / Objective This meta-analysis assessed the correlation between neutrophil-lymphocyte ratio (NLR)/platelet-to-lymphocyte ratio (PLR) and the effectiveness of immune checkpoint inhibitors (ICIs) in non-small cell lung cancer patients (NSCLC). It also indirectly aimed to evaluate the predictive potential of these biomarkers.

Rationale The associations between high NLR/PLR and poor treatment outcomes among NSCLC patients using ICI were reported in some studies with inconsistent results. A previous study systematically searched until 01/2020 and just focused on PD-1/PD-L1 inhibitors. 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.

Condition being studied Although surgery, radiation, and chemotherapy therapies have been significantly improved, the non-small cell lung cancer (NSCLC)NSCLC survival prognosis remains low. In recent years, immune checkpoint inhibitors (ICI) have significantly changed the treatment strategy of NSCLC. Though clinical outcomes have improved, many patients still have poorly responded. Evaluating the efficiency of drugs before prescribing them is a crucial measure to reduce medical expenses, especially in developing nations with constrained budgets. Therefore, finding non-invasive, effective, and low-cost markers to predict treatment outcomes is essential for the improvement of ICI therapeutic efficacy. 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 poor treatment outcomes among NSCLC patients using ICI. These associations were reported in some studies with inconsistent results.

METHODS

Search strategy A systematic search was done until October 2021 on electric 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').

Participant or population Non-small-cell lung patients in the study were treated with immune checkpoint inhibitors monotherapy.

Intervention Immune checkpoint inhibitors monotherapy.

Comparator Not applicable, the study included all available comparators.

Study designs to be included Cohort or case-control.

Eligibility criteria Addition inclusive criteria
• 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.
Exclusive criteria:
• conference abstracts, case reports and case series, meta-analyses, or review articles;
• non-human studies;
• not written in English;
• without full text.

Information sources Electronic databases, including PubMed, The Cochrane Library, and EMBASE.

Main outcome(s) overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and disease control rate (DCR).

Data management 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 into an extraction table. The HR values calculated based on the univariate and multivariate analysis would be collected, and HR values from multivariate analysis models were preferred. All processes of searching, screening, data extraction, and quality assessment were independently performed by two researchers (Tran NKV. and Cuc NTT). Any disparity was solved by a discussion with a third party (Phung TN).

Quality assessment / Risk of bias analysis 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 can be divided into three quality criteria: poor quality (0-2), medium quality (3-5), and good quality (6-9) (McPheeters ML, 2012). The studies with NOS scores over six were included in the meta-analysis.

Strategy of data synthesis 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 I2 and p-value of Cochran's Q test. If there was no heterogeneity (I2 0.1), the fixed effects model would be applied; otherwise, the random effects model would be used (Leandro G., 2005; Huedo-Medina et al., 2006).
If there was heterogeneity between studies, a meta-regression analysis was performed to determine the cause of the heterogeneity.

Publication bias was evaluated based on the asymmetry of the funnel plot and Egger's linear regression test (Leandro G., 2005). 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 (Duval and Tweedie, 2000).
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.

Subgroup analysis The analysis included variables such as study design, geographical area, sample size, time of NLR/PLR collection (time-point), NLR/PLR cut-off values, number of treatments, HR data (available or estimated) and HR origin (the univariate and multivariate analysis), from these, subgroup analysis was performed according to the likely sources of heterogeneity (Michael Borenstein, 2009a).

Sensitivity analysis 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 (Michael Borenstein, 2009b).

Language restriction English.

Country(ies) involved Vietnam.

Keywords immune checkpoint inhibitors; NLR; NSCLC; meta-analysis; PLR.

Contributions of each author
Author 1 - Tran Nguyen Khanh Van - All authors contributed to the study's design and revised the manuscript; author 1 performed the data extraction and the statistical analysis and drafted the manuscript.
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