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The prognostic/ predictive value of the systematic inflammatory response in patients receiving immunotherapy for non-small cell lung cancer: a systematic review and meta-analysis

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Abstract

Background The second most common malignancy after breast cancer is lung cancer (LC). Small cell lung cancer accounts for 15%, while non-small lung cancer (NSCLC) accounts for 85% of cases. Immunotherapy has improved treatment outcomes in NSCLC. However, the role of systemic inflammation-based prognostic scores in predicting response to treatment is not clear. The meta-analyses aims to evaluate the prognostic/ predictive value of inflammatory biomarkers, including NLR, ALI, PLR, CRP, and mGPS, and their potential associated with overall survival in NSCLC patients receiving immunotherapy as first-line or second-line treatment.

Methods A systematic review and meta-analysis was conducted following the Cochrane Handbook and PRISMA guidelines. Searches were performed in PubMed, Cochrane Library, and Web of Science for studies published until January 1, 2022, using specific keywords related to NSCLC, immunotherapy, inflammatory biomarkers and survival. Meta-analysis was performed using RevMan software, analyzing the hazard ratio (HRs) with a 95% confidence interval (CIs) primarily in relation to overall survival.

Results Six thirty three records were identified, and 17 articles were included in the meta-analysis. The pooled analysis of NLR, ALI, PLR, CRP, and mGPS was significantly associated with OS without significant heterogeneity (NLR: HR = 2.15; 95% CI 1.60 – 2.87; *P*-Value < 0.00001); (ALI: HR = 2.03; 95% CI 1.43 – 2.88; *P*-Value < 0.0001); (PLR: HR = 4.06; 95% CI 2.14 – 7.67; *P*-Value < 0.0001); (CRP: HR = 5.37; 95% CI 3.90 – 7.39; *P*-Value < 0.00001); and (mGPS: HR = 3.27; 95% CI 1.26 – 8.28; *P*-Value = 0.01), respectively.

Conclusions Systemic inflammatory biomarkers demonstrate independent prognostic/ predictive value in patients with advanced non-small cell lung cancer who receive immunotherapy as either the first-line or second-line therapy.

Keywords Systemic Inflammation Biomarkers, Overall Survival, Advanced Non-Small Cell Lung Cancers, Immunotherapy, Systematic Review, Meta-Analysis

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Background

With 2.21 million diagnoses and 1.80 million deaths from cancer-related causes in 2020 worldwide, lung cancer (LC) is the second-most frequent malignancy after breast cancer [1]. LC can present as non-small cell lung cancer NSCLC (85% of cases) and small cell lung cancer SCL (15%). Adenocarcinoma (ADC) and squamous cell carcinoma (LSQCC) are the two types of NSCLC identified histologically [2]. The type and stage of the disease greatly impact the treatment and prognosis. NSCLC early-stage can be treated by surgical excision [3]. Although there have been substantial improvements in the oncological care of late-stage NSCLC in recent years, survival rates for most patients are still low because they have an advanced illness at the time of diagnosis (stage III or IV) [3].

Nevertheless, the development of anti-programmed cell death-1 (anti-PD-1) and anti-programmed cell death ligand-1 (anti-PD-1) has significantly changed the treatment landscape for various solid cancers, including NSCLC [4]. This change has a significant beneficial impact on overall survival (OS) and progression-free survival (PFS) [4]. Tumour PD-L1 expression is the most studied biomarker for selecting patients for immunotherapy. PD-L1 expression may determine the efficacy of first-line immunotherapy in patients with advanced NSCLC [4]. Such immune checkpoint inhibitors (ICIs) may be used as a monotherapy or in combination with other traditional therapies like chemotherapy as a first- or second-line treatment for advanced NSCLC [5, 6].

Therefore, it is of interest that meta-analyses have shown that systemic inflammatory response markers are associated with poor prognosis in patients with NSCLC. For example, in more than 7,000 patients, it was shown that a high Glasgow Prognostic Score (GPS) was associated with poor clinical outcomes [7]. Similarly, in more than 1500 patients, the neutrophil–lymphocyte ratio (NLR) was associated with poor clinical outcomes [8]. Although these meta-analyses primarily reflect the prognostic value of markers of the systemic inflammatory response in patients with NSCLC across all disease stages and treatment modalities, they suggest a role for such markers in patients receiving immunotherapy for NSCLC. Indeed, there is some evidence that this may be the case [9, 10].

The meta-analyses aims to evaluate the prognostic/predictive value of inflammatory biomarkers, including NLR, ALI, PLR, CRP, and mGPS, and their potential associated with overall survival in NSCLC patients receiving immunotherapy as first-line or second-line treatment.

Methods

A meta-analysis was conducted using the Cochrane Handbook for Systematic Reviews of Interventions [11]. The report was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12].

Data Sources & Search Strategy

A search was carried out on the following electronic databases: PubMed, Cochrane Library, and Web of Science (WOS) for relevant studies published in the literature and retrieved articles published till 1st January 2022. The complete research strategies and search terms included ((Non-Small-Cell Lung OR NSLC OR lung cancer* OR lung carcinoma* OR lung tumor* OR lung tumor* OR non-small cell*) AND (Immunotherapy and inflammation (CRP + Neutrophils + WCC))). The search included studies reported in English and did not use further search limits. The reference lists of the retrieved articles, including paper citations for potentially relevant papers, were also reviewed.

Eligibility criteria

All studies with the following criteria were included: (1) retrospective observational studies written in English "if written in another language English translation was present"; (2) patients had advanced non-small lung cancer; (3) patients were treated with immunotherapy; and (4) the study should evaluate the overall survival of at least one of systematic inflammatory biomarkers.

Moreover, the exclusion criteria were animal studies, in-vivo & in-vitro studies, clinical trials, case reports, case series, systematic reviews, meta-analyses, clinical study protocols, letters, comments, correspondence, or editorials.

Study selection

The search results were transferred to the EndNote software to screen and remove duplicate studies. The titles and abstracts of the included studies were reviewed according to the inclusion and exclusion criteria. Another reviewer was consulted when there was doubt whether or not to include the study. These reviewers independently screened the full-text articles to resolve any conflict between reviewers.

Data extraction

The data were independently extracted through two excel sheets: 1. Summary (first author name: year of publication, country, study design, total participants, systematic treatment, aim/objectives, and conclusions). 2. Systemic Inflammatory Biomarkers

(Neutrophil-to-lymphocyte ratio (NLR), Advanced lung cancer inflammation index (ALI), Platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), Modified Glasgow Prognostic Score (mGPS)).

NLR was calculated by dividing the number of neutrophils by the number of lymphocytes, often from peripheral blood samples and cells that infiltrate tissue, such as tumour cells. At the same time, PLR is computed by dividing the platelet count by the lymphocytes [10, 13]. ALI was calculated as follows: body mass index (kg/m^2) × serum albumin (g/dL) ÷ NLR. Serum CRP and albumin levels were used to calculate the modified Glasgow prognostic score (mGPS), the modified GPS (mGPS) emphasizes the significance of CRP; if CRP is increased, even patients with abnormal normal albumin levels are given a score of 1 [10, 13].

Data synthesis

Meta-analysis was performed using the Review Manager (RevMan 5.4.1). The hazard ratio (HRs) with a 95% confidence interval (CIs) presented the meta-analysis result for overall survival outcomes. Results with a *P*-value < 0.05 were considered significant in the Z-test. The Chi-square test was used to measure the significance of heterogeneity, a potentially substantial heterogeneity (chi-square test $P < 0.1$). The degree of heterogeneity in a meta-analysis was examined using the I^2 test, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. The I^2 value ranged from 0 to 100%: [0% to 25%: Low heterogeneity, 25% to 50%: Moderate heterogeneity, 50% to 75%: Substantial heterogeneity, and 75% to 100%: High heterogeneity]. Publication bias was identified by performing Egger's test and funnel plot (Supplementary Fig. 1). The HRs and 95% of CIs were directly retrieved from the article. If Several estimates were reported for the same marker, the multivariate estimation was used in preference to the univariate analysis.

Results

After searching the databases, 633 records were identified. Forty-three duplicates were removed, leaving 590 records for the screening process. After the title and abstract screening, five hundred fifty-five records were not considered relevant, leaving 35 full-text articles to be reviewed. Finally, 17 articles were included in the systematic review and the meta-analysis. A PRISMA flow chart illustrates the study selection process (Fig. 1).

The neutrophil-to-lymphocyte ratio (NLR)

Meta-analysis of thirteen studies showed a significant association between NLR and overall survival (HR = 2.87; 95% CI 1.91 – 4.30; *P*-Value < 0.00001) with a moderate degree of heterogeneity (*P*-Value = 0.002; $I^2 = 61\%$) (Fig. 2-A). The heterogeneity was reduced by omitting five studies (*P*-Value = 0.21; $I^2 = 28\%$), and the association was still significant (HR = 2.15; 95% CI 1.60 – 2.87; *P*-Value < 0.00001) (Fig. 2-B). The possibility of publication bias was related to the method and the high intensity of retrospective studies (Supplementary Fig. 1). Meta-analysis of thirteen studies showed that NLR with a threshold of ≥ 5 in five studies [14–19], NLR > 5 in four studies [20–23], NLR ≥ 4 in two studies [23, 24], and identified as high vs low in one study [25].

Advanced lung cancer inflammation index (ALI)

The forest plot of four studies showed a significant association between ALI and overall survival (HR = 1.72; 95% CI 1.22 – 2.43; *P*-Value = 0.002) with a moderate degree of heterogeneity (*P*-Value = 0.15; $I^2 = 44\%$) (Fig. 3-A). The heterogeneity was reduced by omitting one study (*P*-Value = 0.27; $I^2 = 23\%$), and the association became more significant (HR = 2.03; 95% CI 1.43 – 2.88; *P*-Value < 0.0001) (Fig. 3-B).

The forest plot of four studies showed that ALI with a threshold of > 18 in two studies [17, 20], ALI ≥ 18 in one study [26], and ALI < 18 in one study [15].

Platelet-to-lymphocyte ratio (PLR)

The pooled analysis of six studies showed a significant association between PLR and overall survival (HR = 4.06; 95% CI 2.14 – 7.67; *P*-Value < 0.0001) without heterogeneity (*P*-Value = 0.23; $I^2 = 28\%$) (Fig. 4). The pooled analysis of six studies showed that PLR with a threshold of > 262 in three studies [18, 21, 22] and identified as high vs low in three studies [14, 17, 23].

C-reactive protein (CRP)

The forest plot of seven studies showed a significant association between CRP and overall survival (HR = 4.22; 95% CI 2.14 – 8.31; *P*-Value < 0.0001) with a high degree of heterogeneity (*P*-Value < 0.00001; $I^2 = 82\%$) (Fig. 5-A). The heterogeneity was solved by omitting one study (*P*-Value = 0.80; $I^2 = 0\%$), and the association became more significant (HR = 5.37; 95% CI 3.90 – 7.39; *P*-Value < 0.00001) (Fig. 5-B). The forest plot of seven studies showed that CRP with a threshold of ≥ 10 mg/l in three studies [26–28], CRP > 8.9 mg/l in one study [22], CRP ≥ 26 mg/l in one study [18], CRP > 50 mg/l in one study [29], and identified as high vs normal in one study [17].

Modified Glasgow Prognostic Score (mGPS)

The pooled analysis of four studies showed a significant association between mGPS and overall survival (HR = 3.27; 95% CI 1.26 – 8.28; *P*-Value = 0.01) without

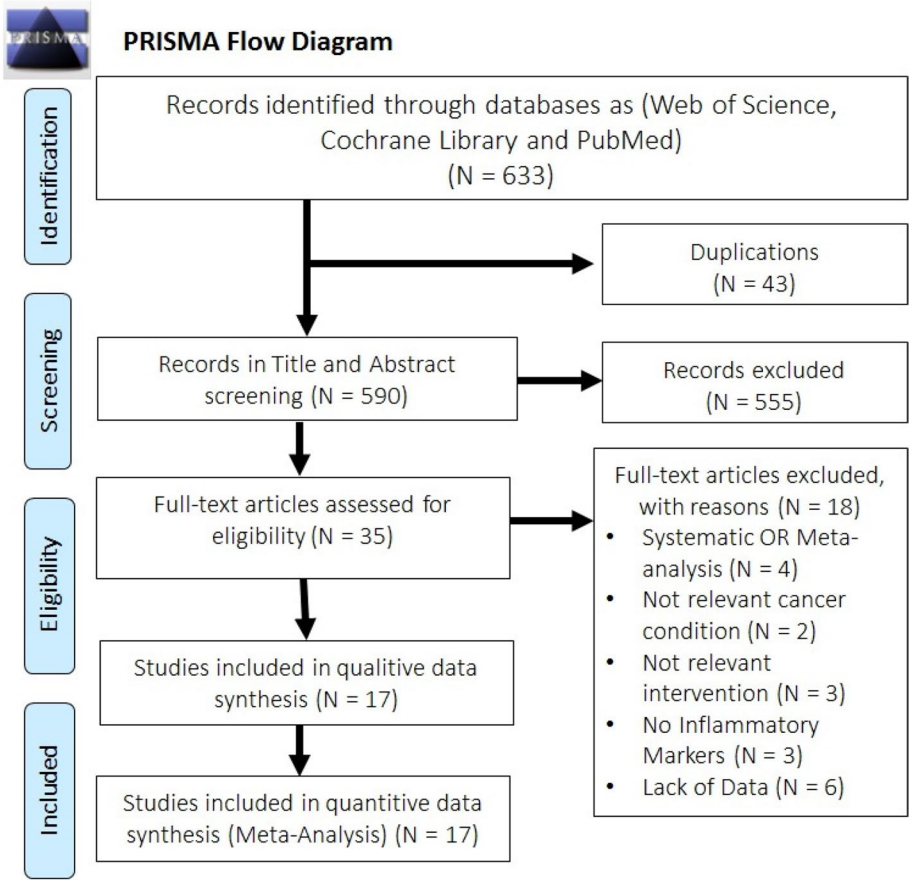

Fig. 1 PRISMA Flow Chart

heterogeneity (*P*-Value = 0.28; $I^2 = 23\%$) (Fig. 6). The pooled analysis of four studies showed that mGPS with a threshold of ≥ 1 in three studies [15, 29, 30] and identified as high vs low in one study [14].

Discussion

The present meta-analyses showed that inflammatory biomarkers, including NLR, ALI, PLR, CRP, and mGPS, were significantly independently associated with overall survival in NSCLC patients, highlighting their role as prognostic factors and potential predictive factors for efficacy in patients with NSCLC receiving immunotherapy. Specifically, an elevated systemic inflammatory response, however, measured, was associated with poorer treatment efficacy and overall survival, either as second-line or first-line therapy. Furthermore, the predictive efficacy of ALI [20] and mGPS [31] specifically examined treatment efficacy confirming the relationship between immunotherapy efficacy and overall survival in patients with NSCLC. Therefore, the systemic inflammatory response has considerable potential to select patients likely to benefit from immunotherapy. However, it remains to be determined which systemic inflammation-based prognostic score should be used, their optimal threshold, and the implications in clinical practice. Nevertheless, markers of the systemic inflammatory response should be routinely measured alongside established prognostic factors in these patients.

The present meta-analysis of thirteen studies showed a significant association between NLR and overall survival (HR = 2.87; 95% CI 1.91 – 4.30; *P*-Value < 0.00001) with a moderate degree of heterogeneity (*P*-Value = 0.002; I2 = 61%). NLR pooled analysis of immunotherapy in Wang et al. [32] study also showed a significant association between NLR and overall survival (HR = 2.50; 95% CI 1.60 – 3.89; *P*-Value < 0.0001) with a high degree of heterogeneity ($I^2 = 79.9\%$). NLR pooled analysis of Chemotherapy and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor treatment in Chan et al. [33] study showed a significant association between NLR and overall survival (HR = 1.97; 95% CI 1.56 – 2.49; *P*-Value < 0.00001) without heterogeneity ($I^2 = 12\%$). NLR pooled analysis of immunotherapy in Platini. et al. [34] study showed a significant association between

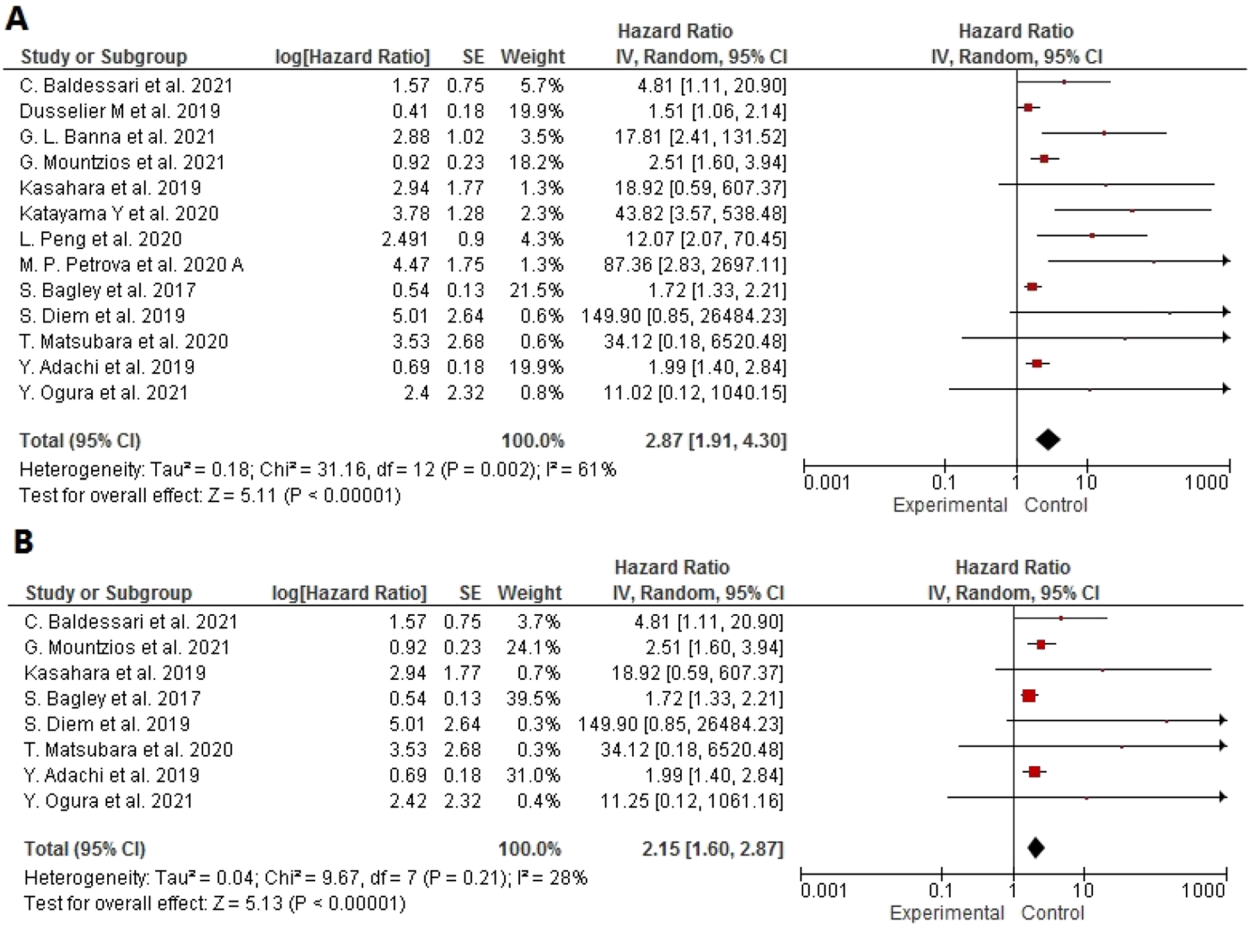

Fig. 2 The neutrophil-to-lymphocyte ratio (NLR)

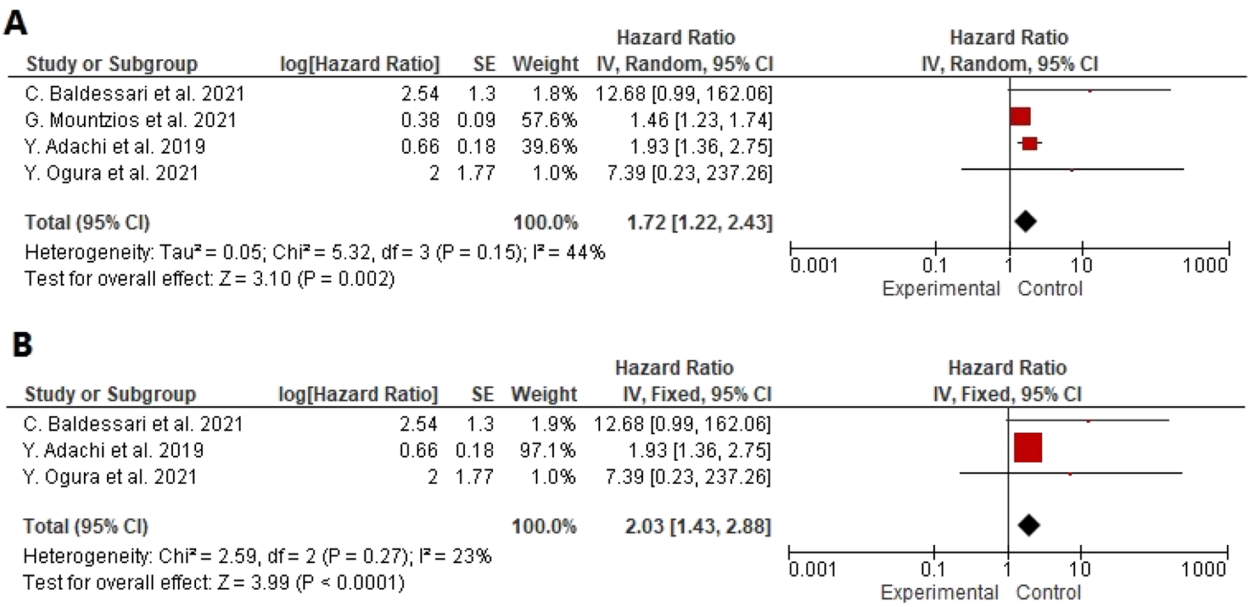

Fig. 3 Advanced lung cancer inflammation index (ALI)

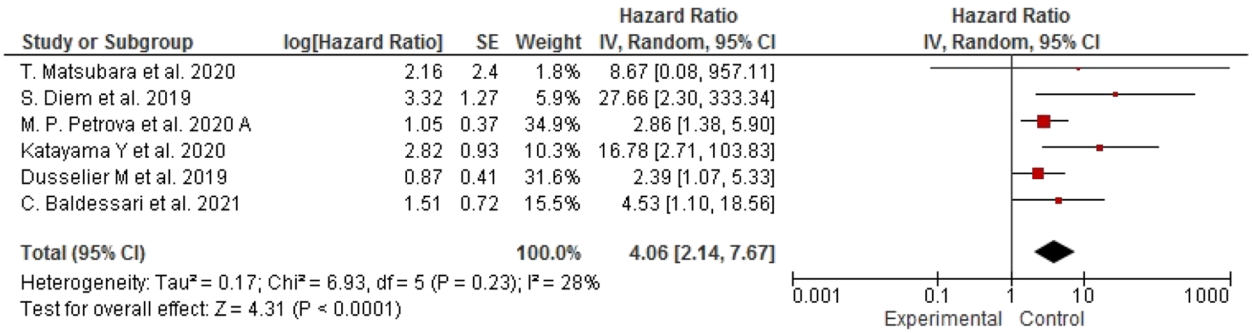

Fig. 4 Platelet-to-lymphocyte ratio (PLR)

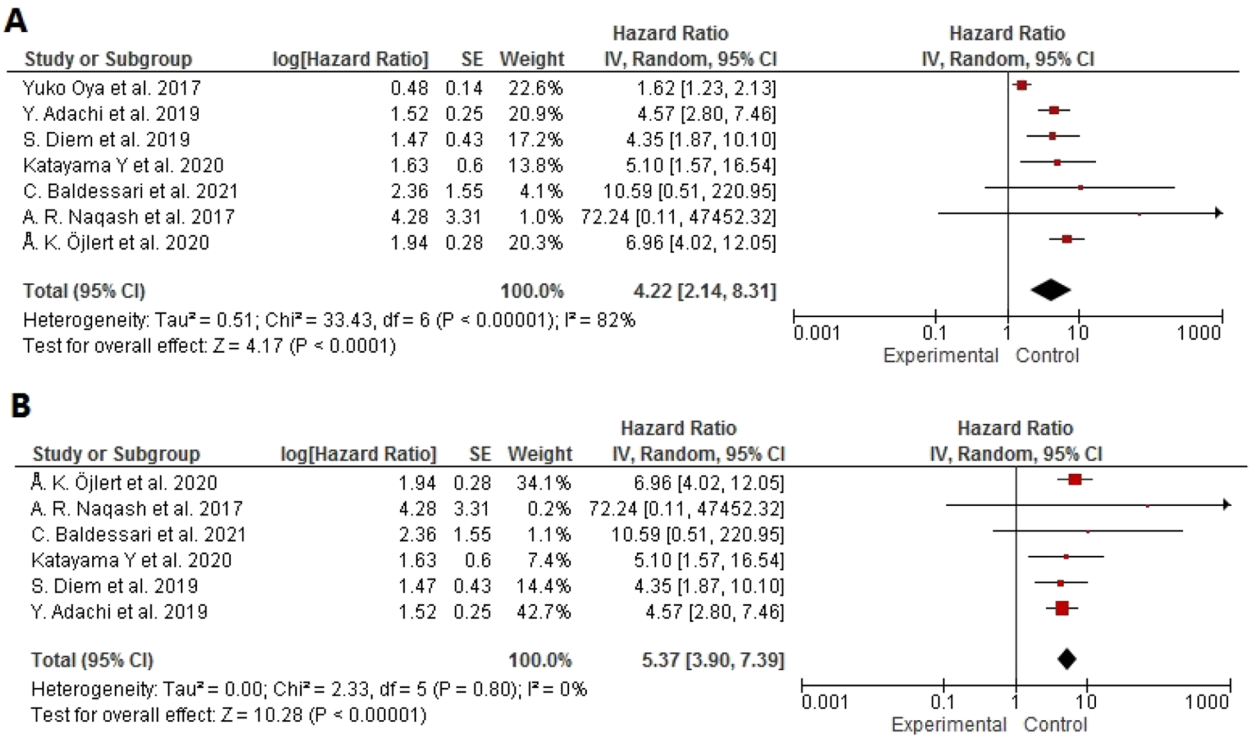

Fig. 5 C-reactive protein (CRP)

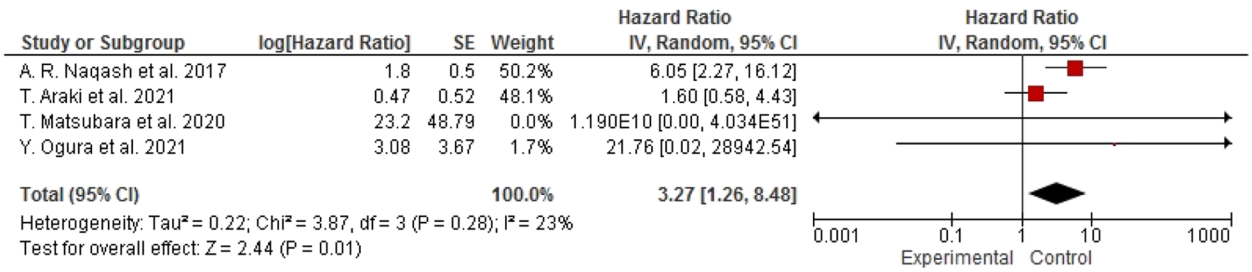

Fig. 6 Modified Glasgow Prognostic Score (mGPS)

NLR and overall survival (HR = 2.68; 95% CI 2.24 – 3.21; *P*-Value < 0.00001) without heterogeneity ($I^2 = 17\%$). Therefore, there would appear to be consistent evidence that NLR has prognostic value.

The present meta-analysis of six studies showed a significant association between PLR and overall survival (HR = 4.06; 95% CI 2.14 – 7.67; *P*-Value < 0.0001) without heterogeneity (*P*-Value = 0.23; $I^2 = 28\%$). PLR pooled analysis of immunotherapy in Platini et al. [34] study showed a significant association between PLR and overall survival (HR = 2.14; 95% CI 1.72 – 2.67; *P*-Value < 0.00001) with mild heterogeneity ($I^2 = 37\%$). PLR pooled analysis of immune checkpoint inhibitors in NSCLC Patients in Xu et al. [35] study showed a significant association between PLR and overall survival (HR = 1.52; 95% CI 1.27 – 1.82; *P*-Value < 0.00001) without heterogeneity ($I^2 = 0\%$). While PLR pooled analysis of Chemotherapy and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor treatment in Chan et al. study [33] showed a non-significant association between PLR and overall survival (HR = 0.87; 95% CI 0.62 – 1.22; *P*-Value = 0.41) without heterogeneity ($I^2 = 0\%$). Therefore, there would appear to be inconsistent evidence that PLR has consistent prognostic value.

Furthermore, across a variety of common solid tumours treated with immunotherapy, an increase in NLR at six weeks from baseline was significantly associated with shorter OS (HR, 4.11; 95% CI, 1.86 – 9.11; $P < 0.001$) in patients with melanoma, gastrointestinal, lung, or head and neck cancers (20.0%) [36, 37]. Similarly, GPS has been shown to have prognostic value in such solid tumours [38, 39]. These observations align with those made more generally in patients with advanced cancer [40]. Indeed, the combination of ECOG-PS and mGPS is a powerful prognostic framework and has been used extensively in patients with advanced cancer, including NSCLC [41, 42]. ECOG-PS is the most widely validated prognostic indicator in patients with advanced cancer. However, it is a subjective measure, prone to interindividual variation and overestimation compared with the patient assessment. Therefore, combining the subjective ECOG-PS with the objective systemic inflammation-based prognostic score (NLR, mGPS) is an important step forward in the treatment allocation and should form the basis of future stratification of patients receiving immunotherapy. Although greater tumour cell molecular characterization leads to greater stratification of NSCLC and different treatment pathways and outcomes (e.g., EGFR, ALK-driven NSCLC), the present work highlights the importance of the host systemic inflammatory response in this tumour type and immunotherapy treatment. Therefore, it will be important that future randomized trials of immunotherapy, in particular in NSCLC, include measures of the systemic inflammatory response so that the prognostic importance of the tumour and host is better understood.

The present systematic review and meta-analysis have limitations inherent to the methodology. In particular, there were few prospective studies in the present study, the majority being retrospective analyses of datasets. In the present meta-analysis, the thresholds of each index were not completely consistent and therefore this may have introduced error into the pooled analysis. In particular, with the NLR studies, there were different thresholds were applied across the studies, and it would be important that there is threshold standardization in future prospective studies. However, this is a feature of the evolving literature to date, except for the mGPS, and has not been addressed in previous meta-analysis. Indeed, the problem may be compounded with composite scores such as the systemic inflammatory response index (SIRI) that uses the combination of neutrophils, lymphocytes and monocytes such that an abnormal threshold be generated by values of neutrophils, lymphocytes or monocytes in the normal range [43, 44]. Also, with threshold standardization, the degree of heterogeneity may decrease in future systematic reviews and meta-analyses.

The date of the present comprehensive literature search was 1st January 2022 and this is an area of considerable ongoing interest. Nevertheless, the present study identified that of all the systemic inflammation based prognostic scores NLR and mGPS were the most consistent prognostic/ predictive factors. Therefore, future work should focus on these markers. Recently, a meta-analysis of the relationship Glasgow Prognostic Score and outcome in NSLC patients treated with immunotherapy was carried out confirming the present results [45]. Specifically, the pooled results indicated that a higher baseline mGPS was associated with poorer OS and PFS in non-small cell lung cancer patients treated with immune checkpoint inhibitors and these findings were robust after subgroup and sensitivity analyses. However, with only 7 studies and 833 patients were identified and further work is required.

Conclusions

The present systematic review and meta-analysis showed that markers of the systemic inflammatory response, particularly the Neutrophil-to-Lymphocyte Ratio (NLR) and the modified Glasgow Prognostic Score (mGPS), possess significant clinical prognostic/ predictive value in patients with NSCLC undergoing immunotherapy. Given their ability to be measured easily in routine clinical practice, these markers can serve as effective tools for risk stratification and personalized treatment planning. By incorporating NLR and mGPS into clinical decision-making, healthcare providers may better allocate

treatment resources, potentially improving patient outcomes and optimizing therapeutic strategies in this challenging patient population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13822-9.

Supplementary Material 1.

Authors' contributions

RS: Conceptualization, software, data collection, data curation, analysis, writing- reviewing and editing, SM: Formal analysis, supervision, reviewing and editing. AC: reviewing and editing. DM: Project administration, visualization, methodology, reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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