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Prognostic value of blood eosinophils for predicting survival and treatment outcomes in people with non-small cell lung cancer (Protocol)

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Prognostic value of blood eosinophils for predicting survival and treatment outcomes in people with non-small cell lung cancer (Protocol).
Cochrane Database of Systematic Reviews 2025, Issue 2. Art. No.: CD015783.
DOI: 10.1002/14651858.CD015783.

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[Prognosis Protocol]

Prognostic value of blood eosinophils for predicting survival and treatment outcomes in people with non-small cell lung cancer

Hugues Sultana[1], Tom De Vos[1], Reem Malouf[2], François Calais[3], Corynne Marchal[4], Guillaume Eberst[1,5], Virginie Westeel[1,6], Cindy Barnig[1,6]

[1]Chest Disease Department, University Hospital, Besançon, France. [2]Nuffield Department of Population Health, Big Data Institute (BDI), University of Oxford, Oxford, UK. [3]Health Sciences University Library, Marie & Louis Pasteur University, Besançon, France. [4]Marie & Louis Pasteur University, Besançon, France. [5]Marie & Louis Pasteur University, University Hospital, EFS, INSERM, UMR RIGHT, Besançon, France. [6]Marie & Louis Pasteur University, University Hospital, EFS, INSERM, UMR RIGHT, Besançon, France

Contact: Cindy Barnig, cbarnig@chu-besancon.fr.

Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 2, 2025.

Citation: Sultana H, De Vos T, Malouf R, Calais F, Marchal C, Eberst G, Westeel V, Barnig C. Prognostic value of blood eosinophils for predicting survival and treatment outcomes in people with non-small cell lung cancer (Protocol). *Cochrane Database of Systematic Reviews* 2025, Issue 2. Art. No.: CD015783. DOI: 10.1002/14651858.CD015783.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (prognosis). The objectives are as follows:

To assess the prognostic value of measuring pretreatment baseline blood eosinophil levels in adults receiving systemic treatment for any stage of non-small cell lung cancer.

BACKGROUND

Description of the health condition and context

Lung cancer is the second most common cancer worldwide, with more than two million new cases diagnosed in 2020, according to GLOBOCAN (Global Cancer Observatory) [1]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80% to 85% of all cases [2]. The two predominant NSCLC histological phenotypes are adenocarcinomas (50%) and squamous cell carcinomas (25%) [3]. According to the Surveillance, Epidemiology and End Results (SEER) programme in the USA, 57% of lung cancers are diagnosed at a locally advanced or metastatic stage (stage IV) [2]. Consequently, lung cancer survival is poor when compared to other cancers, with a five-year overall survival of less than 20% [4].

Lung cancer treatment depends on the stage at which the disease is detected, its histological type and the presence of oncogenic driver mutations (genetic alterations that directly contribute to oncogenesis).

For people with early-stage NSCLC (stage I or II), the standard treatment is surgery, provided that the person has adequate cardiopulmonary function [5].

For people with resected (i.e. surgically removed) NSCLC at stages IIA and III, adjuvant chemotherapy is recommended, depending on the stage as reported in the Tumour, Node, Metastasis (TNM) staging system [6, 7].

For those with unresectable disease, treatment for locally advanced NSCLC (stage III) is based on chemoradiotherapy. This usually includes two to four courses of platinum-based chemotherapy, combined with radiotherapy at a dose of 66 gray (Gy). Concomitant chemoradiotherapy is recommended for people with an ECOG (Eastern Cooperative Oncology Group) Performance Status (PS) of 0 or 1, without any comorbidity and who are under 70 years old (the assessment of PS in people diagnosed with cancer provides information about their ability to perform daily activities and overall functional well-being and is used to guide treatment intervention). For other patients, the treatment is sequential [8]. After completing the initial phase of combined radiotherapy and chemotherapy, starting treatment with immunotherapy - immune checkpoint inhibitors (ICIs) within 42 days is generally recommended. ICIs are therapies designed to block immune checkpoint pathways exploited by cancer cells to evade immune surveillance. This treatment is typically given for up to 12 months [9].

Finally, treatment for people with metastatic/advanced NSCLC (stages III and IV) has been marked by significant therapeutic progress in the last decade, in particular, by the development of ICIs. These therapies have been utilised in the first- and second-line settings (i.e. both for those who have not received prior treatment and those who have already undergone treatment), and have led to unprecedented prolonged survival for some patients [10, 11]. Yet, the success of ICIs in the treatment of lung cancer is not without major challenges. Indeed, nearly 70% of people with advanced NSCLC do not derive lasting benefit from ICI-based therapies [12]. The current therapeutic standard remains the combination of chemotherapy (platinum-based and pemetrexed for non-squamous NSCLC or carboplatinum and paclitaxel for squamous NSCLC) and immunotherapy. The precise mechanism of action for immunotherapy targeting programmed cell death protein 1/programme cell death-ligand 1 (PD-1/PD-L1) checkpoints involves releasing the "brakes" on the immune system. Normally, the PD-1 protein on T cells binds to the PD-L1 protein on cancer cells, inhibiting the immune attack. By blocking this interaction, PD-1/PD-L1 inhibitors enable T cells to recognise cancer cells and more effectively destroy them. In people over 70 years of age with a PD-L1 level of expression above 50%, immunotherapy as a single-agent treatment has demonstrated significant efficacy, offering a well-tolerated and effective treatment option that aligns with the specific needs of older patients [11, 13].

Description of the prognostic factor

Eosinophils were first described in 1879 by Paul Ehrlich. Eosinophils are bone-marrow-derived leukocytes that are released into the peripheral blood in a phenotypically mature state, where, in a person in good health, they represent less than 5% of the total leukocyte population or less than 500 cells per cubic millimetre of blood. Morphologically, they are characterised by a bilobed acidophilic nucleus and cytoplasmic granules. Eosinophils can release a broad range of mediators, including basic proteins, enzymes, cytokines, chemokines and growth factors. Eosinophils express on their surface a broad range of receptors, allowing them to interact with many agents of the inflammatory response.

Eosinophils are part of innate immunity, and, traditionally, have been considered as end-stage destructive cells involved in host protection against parasites and immunopathology of asthma and allergic disease [14]. More recently, it has been shown that eosinophils can also contribute to the immune response to cancer [15]. However, the precise role of eosinophils in cancer is not fully understood, and both pro- and anti-tumourigenic activities have been reported in pre-clinical models [16, 17].

On the pro-tumourigenic side, eosinophils may facilitate tumour progression through mechanisms such as immunosuppression, mediated by proteins like indoleamine 2,3-dioxygenase (IDO); angiogenesis, driven by factors like vascular endothelial growth factor (VEGF), and interleukin-8 (IL-8); and direct promotion of tumour growth via proteins such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF). Conversely, eosinophils can exert antitumoural effects through cytotoxic actions mediated by Major Basic Protein (MBP) or Eosinophil Peroxidase (EPX), the polarisation of macrophages towards an M1 anti-tumour phenotype and the recruitment of CD8+ T cells through chemokine signalling.

In people with NSCLC, increased blood eosinophil levels and eosinophilic tumour infiltration have been observed [18].

Health outcomes

In the field of thoracic oncology, there are a number of parameters that help clinicians to determine the efficacy of treatment. The most important parameter is overall survival (OS), defined as the period from the start of treatment to death from any cause.

The second, more easily measured parameter is progression-free survival (PFS), defined as the period from the start of treatment to clinical or radiographic progression or death from any cause. However, it is important to note that an improvement in progression-free survival is not correlated with an improvement

in overall survival. Another important measure is the evaluation of both the efficacy of a treatment and its tolerance, called time-to-treatment-failure (TTF), which is defined as the period from the start of a treatment to discontinuation from any cause or last follow-up.

Another criterion of interest is the objective response rate (ORR), commonly assessed in phase II studies. It represents the proportion of people who exhibit any of the predefined responses to therapy, as determined by the first re-evaluation using computed tomography based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [19]. These responses are categorised into four distinct types: complete response, partial response, progression, and stability.

Finally, it is always important and useful to predict the safety of a treatment. In assessing treatment safety, two key aspects are considered: immune-related adverse events (IRAEs) arising from ICI cancer therapy and adverse events of any grade (AEs).

Why it is important to do this review

In thoracic oncology, the field of application of biomarkers is vast: prediction of the risk of developing cancer, detection of early forms of cancer, prediction of treatment response and tolerance to treatment, and detection of the risk of tumour recurrence. Consequently, biomarkers help to better select people for treatment by identifying those likely to develop side effects and those at risk of not responding to the prescribed treatment.

In recent years, studies have suggested that blood eosinophilia may be of interest as a prognostic biomarker of treatment response in lung cancer patients [20]; however, studies have also highlighted the risk of AEs [21]. Current treatments indicated for non-small cell lung cancer, such as chemotherapy and immunotherapy, have shown variable responses in lung cancer patients. Therefore, it is important to identify prognostic biomarkers to predict the success of administered treatments as well as their safety.

Blood eosinophils have been studied for their potential prognostic value in NSCLC, although most of the clinical data provided is heterogenous. A recent narrative synthesis linked blood eosinophils to clinical outcomes and immune-related side effects in people treated with PD-1/PD-L1 checkpoint inhibitors, but no quantitative synthesis of outcomes is available [22]. As lung cancer patients undergo regular blood testing, identifying the prognostic role of circulating eosinophils could be of major interest. Therefore, a systematic review that evaluates the prognostic value of blood eosinophils in lung cancer could have important clinical implications and the potential to improve patient management.

OBJECTIVES

To assess the prognostic value of measuring pretreatment baseline blood eosinophil levels in adults receiving systemic treatment for any stage of non-small cell lung cancer.

METHODS

Criteria for considering studies for this review

Our review will focus on evidence for the prognostic value of increased baseline blood eosinophil levels in people with NSCLC who are receiving systemic treatment (drugs that act throughout the body via the bloodstream), such as chemotherapy and/or immunotherapy (but excluding targeted therapies, which are treatments specifically targeting molecular changes and/or proteins driving tumour growth).

Concept	Definition
Population	People (≥ 18 years of age) with any stage of non-small cell lung cancer (NSCLC) receiving systemic treatment (excluding targeted therapies)
Index prognosis factor	Elevated baseline blood eosinophil levels
Control	Non-elevated baseline blood eosinophil levels
Outcomes	• Overall survival (OS) • Objective response rate (ORR) • Progression-free survival (PFS) • Time to treatment failure (TTF) • Immune-related adverse events (IRAEs) • Adverse events of any grade (AEs) At any follow-up time
Timing	Baseline blood eosinophil levels are assessed prior to the initiation of treatment.
Setting	Any clinical settings in any geographical locations

Types of studies

We will include retrospective or prospective cohort studies. The studies should include a measurement of blood eosinophil levels at baseline. Given the prognostic nature of our objective, we will include studies with any follow-up period.

We will exclude research articles that are not based on original data (e.g. letters to the editor, expert opinions, narrative reviews). We will exclude preclinical research that is not based on original data, as well as preclinical animal and basic research. We will also exclude case reports and prospective case series studies with fewer than 20 participants. No studies will be excluded based on the language of publication.

Population of interest

We will include studies involving adults (≥ 18 years of age) with any stage of NSCLC, according to the 8th edition of the TNM classification [7], and who are undergoing systemic therapy, including chemotherapy and/or immunotherapy such as inhibitors targeting PD-L1/PD-1 checkpoints expressed by cancer and immune cells. We will exclude people receiving targeted therapy, which involves treatments that specifically target oncogenic drivers such as EGFR (epidermal growth factor receptor), ALK (anaplastic lymphoma kinase) and ROS (repressor of silencing) in cancer cells. These therapies work by directly inhibiting the specific mutations or proteins that drive cancer growth. Because these targeted therapies lead to significantly different treatment responses and prognoses compared to other treatments, individuals on these therapies will be excluded from our review.

Types of prognostic factors

We will study the association between blood eosinophil levels prior to the initiation of treatment (i.e. measured at baseline) and the survival outcomes regardless of treatment strategies.

We will include studies reporting eosinophil levels as either the absolute eosinophil count (AEC), measured as the number of eosinophils per ml or per mm^3, or the relative eosinophil count (REC), which represents the percentage of eosinophils amongst all white blood cells. Given that the threshold for increased eosinophil levels may differ across studies, we will adopt the definition of increased blood eosinophil levels as specified by each individual study.

Types of outcomes to be predicted

Primary outcome

- Overall survival (OS) at any follow-up time: defined as the period from the start of treatment to death from any cause

Secondary outcomes

- Objective response rate (ORR) at any follow-up time: defined as the proportion of participants who had a partial or complete response to therapy. This should be assessed at first re-evaluation by computed tomography, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [19], and categorised into four distinct responses: complete response, partial response, progression or stability.
- Progression-free survival (PFS) at any follow-up time: defined as the period from the start of treatment to clinical or radiographic progression or death from any cause
- Time to treatment failure (TTF) at any follow-up time: defined as the period from the start of the treatment to discontinuation from any cause or last follow-up
- Immune-related adverse events (IRAEs) at any follow-up time: defined as the occurrence of autoimmune diseases that can affect any organ of the body after the administration of an immune checkpoint inhibitor
- Adverse events of any grade (AEs) at any follow-up time: defined as the occurrence of any toxicity secondary to the administration of systemic therapy (Common Terminology Criteria for Adverse Events (CTCAE)).

Search methods for identification of studies

Electronic searches

We will search for relevant studies in the following databases; we will apply no language restrictions.

1. MEDLINE (accessed via PubMed) from 1951 to present
2. Embase (accessed via Elsevier) from 1947 to present

We will perform the electronic searches according to the recommendations of the Cochrane Methods Prognosis Group. The search strategies for MEDLINE and Embase are shown in Supplementary material 1.

Searching other resources

We will handsearch the references of eligible studies to identify additional studies for inclusion.

We will consult experts on the topic (including authors of the included studies) to identify any additional, unreported or ongoing studies.

We will use the Web of Science database from Clarivate (clarivate.com/products/web-of-science) to identify articles that could have cited the primary reference for each of our included studies.

In order not to miss any potential publications that may not have been referenced in the main databases, we will search the meeting abstracts of conferences from the following sources.

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- European Respiratory Society (ERS)
- American Thoracic Society (ATS)

We will collect clinical study reports about checkpoint inhibitors from the US Food and Drug Administration (FDA) (https://www.fda.gov/) and European Medicines Agency (EMA) websites (https://www.ema.europa.eu/en).

Data collection

Selection of studies

Using Covidence [23], two review authors (HS and TDV) will independently screen the titles and abstracts of records retrieved by the searches. The same review authors will also screen and

check the full text of the studies deemed to be relevant from the initial screening against the review eligibility criteria. Any disagreement will be resolved through discussion, or by consulting a third review author (GE or CB) if required.

If there is missing information or if we need any further clarification, we will contact the study authors.

We will present the process of study selection in a PRISMA study flow diagram [24]. We will also report the reasons for our exclusions at the full-text screening stage.

Data extraction and management

We will develop a data extraction form (see Supplementary material 2) in accordance with the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies [25], which we will adapt for prognostic factor studies [26]. Using this form, two review authors (HS and TDV) will independently extract relevant data from the included studies. Any disagreement will be resolved through discussion, or by consulting a third review author (GE or CB) if required.

We will extract data for the following domains and items.

Source of data: cohort, case-control, randomised trial participants or registry data

Participants

- Participant eligibility and recruitment method: consecutive participants, location, number of centres, setting, inclusion and exclusion criteria
- Participant description: sex, ECOG performance status, smoking status, mutational status, histologic subtype, PD-L1 TPS (tumour proportion score, %)
- Details of treatments received: type of systemic treatment, line of treatment, G-CSF (granulocyte-colony stimulating factor) administration
- Study dates

Outcome(s) to be predicted: definition and method for measurement of outcome(s), type of outcome(s), time of outcome(s), occurrence, or summary of duration of follow-up

Prognostic factors

- Baseline blood eosinophil levels
- Definition and method for measurement of the prognostic factor of interest eosinophil blood count
- Timing of the prognostic factor measurement: at baseline prior to the initiation of treatment

Sample size: calculation, number of participants, outcomes and events

Missing data: number of participants with any missing value, details of attrition (loss to follow-up); for time-to-event outcomes: number of censored observations and handling of missing data

Analysis: modelling method, model assumptions, unadjusted and adjusted prognostic effect estimates

Results: we will extract adjusted and unadjusted effect estimates (e.g. hazard ratio (HR), odds ratio (OR), risk ratio (RR), mean difference (MD)) and their measures of uncertainty (standard errors (SE), standard deviation (SD), variances, or confidence intervals (CIs) of the prognosis factor-eosinophil counts) for the following outcomes: OS, ORR, PFS, TTF, IAEs and AEs of any grade.

We will list all factors adjusted for all outcomes in the analysis.

Interpretation of presented results, comparison with other studies, discussion of generalisability, strengths and limitations of each study

Assessment of risk of bias in included studies

Two review authors (HS and TDV) will independently assess the risk of bias of each of the included studies using the Quality In Prognosis Studies (QUIPS) tool [27], as recommended by the Cochrane Prognosis Methods group [28] (see Table 1). We will solve disagreements by discussion or by consulting a third review author (GE or CB). We will assess the risk of bias using an Excel sheet [29]. We will rate the risk of bias for the six risk of bias domains of the QUIPS tool: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. We will consider the following 'signalling items'.

1. Study participation domain

- Adequate description of the target population source: the source of the population cohort with NSCLC is clearly described, including the number of centres, the setting and the location.
- Method used to identify the population: this includes a clear description of the study's sampling frame, for example, whether it is convenience, random or stratified sampling, and the recruitment methods, for example, by referral.
- Recruitment period: the start and the end of the study enrolment period are stated in the study.
- Place of recruitment: the institution is stated, for example, whether it is a health centre or hospital.
- Inclusion and exclusion criteria: information related to the NSCLC stage and treatment is described.
- Adequate study participation: the study clearly states how the sample size was determined and whether a sample size calculation is provided.
- Baseline characteristics: the study reports on key participant characteristics such as sex, smoking status, mutational status or histologic subtype.

2. Study attrition domain

- Proportion of baseline sample available for analysis: response rate is adequate, with more than 80% of the study sample providing outcome data.
- Attempts to collect information on participants who dropped out are made.
- Reasons for loss to follow-up and the potential impact on study findings of participants lost to follow-up are provided.
- Outcome and prognostic factor information on those lost to follow-up: key characteristics of participants lost to follow-up are adequately described (e.g. age, sex/gender, smoking status). There are no important differences between key characteristics

and outcomes between participants who completed the study and those who did not.

3. Prognostic factor measurement domain

- Definition of prognostic factor (PF): a clear definition or description of PF is provided (e.g. a clear definition of the threshold value or the continuous variable of eosinophilia level).
- Valid and reliable measurement of PF: the method for measuring eosinophilia in the blood is sufficiently valid and reliable.
- Method and setting of PF measurement: the method and setting of measurement of PF is the same for all study participants.
- Proportion of data on PF available for analysis: more than 80% of the study sample has complete data for eosinophilia counts.
- Method used for missing data: appropriate methods of imputation are used for missing eosinophilia count data.

4. Outcome measurement domain

- Definition of outcomes: a clear definition of the outcome is provided, including duration of follow-up time.
- Valid and reliable measurement of outcome: the method of outcome measurement used is valid and reliable, in order to limit misclassification bias (e.g. blind measurement and confirmation of outcome with a valid and reliable test).
- Method and setting of outcome measurement: the method and setting of outcome measurement is the same for all study participants.

5. Other prognostic factors (covariates) domain

- Important covariates measured: all potential covariates are adjusted for in the analysis. These include the following.
  - Active asthma: several asthma phenotypes have been distinguished, according to their clinical or physiological characteristics, their triggering factors or the type of inflammation involved. Some asthma phenotypes are associated with elevated eosinophilia.
  - Active allergy: moderate eosinophilia may be associated with allergic diseases.
  - Active parasitosis: during a helminth infection, eosinophil activation may occur, resulting in a rise in blood eosinophil levels.
  - Granulocyte-colony stimulating factor (G-CSF): in some individuals, G-CSF may induce a mild increase in the number of circulating eosinophils compared to baseline.
  - Other confounders that are addressed in the included studies and may impact eosinophil levels, such as age, sex, line of treatment and stage of cancer.
- Definition of the confounding factor: clear definitions of the important confounders measured are provided (e.g. asthma severity, stage of cancer).
- Valid and reliable measurement of confounders: measurement of all important confounders is valid and reliable.
- Method and setting of confounding measurement: the method and setting of confounding measurement are the same for all study participants.
- Method used for missing data: if imputation is used for missing confounder data, appropriate methods are used for this.
- Appropriate accounting for confounding: there is sufficient presentation of data to assess the adequacy of the confounder in the study design and the analysis (by including potential confounders in the multivariate regression analysis).

6. Statistical analysis and reporting domain

- Presentation of analytical strategy: there is sufficient presentation of data to assess the adequacy of the analysis, i.e. HR, OR, RR, MD, including the CIs or SEs.
- Model development strategy: the strategy for model building (i.e. inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model, and the selected statistical model is adequate for the design of the study, such as univariate and multivariate logistic regression, Cox proportional hazard models.
- Reporting of results: there is no selective reporting of results.

The operational guide for the QUIPS tool is presented in Supplementary material 3.

For each signalling question, the answer will be yes, no or unclear. For each domain, we will judge whether the study is at low, moderate or high risk of bias, according to the criteria set out in the tool.

Measures of association or predictive performance measures to be extracted

For the primary outcome

Overall survival (OS): we will extract the uninvariate unadjusted and adjusted HR, RR or OR with 95% CI. We will aim to extract adjusted HRs when possible across the studies. When the adjusted HR is not reported, we will extract the unadjusted HR. When the HRs are adjusted for different sets of variables, we will extract all relevant HRs. When HR is not reported, we will try to calculate it using Kaplan-Meier survival curves and the dedicated methods of Parmar and Tierney [30, 31]. The RRs and ORs will be extracted if the HRs are not reported. When possible, we will extract the adjusted HR and 95% CI between the OS and the eosinophil count.

For secondary outcomes

Objective response rate: whether the response is categorised as complete, partial, progression or stability according to the Response Evaluation Criteria in Solid Tumor [19], we will extract adjusted OR or RR with 95% CI between the ORR and prognostic factor-eosinophils count. When the adjusted OR or RR is not reported, we will extract the unadjusted measure of associations. When adjusting to multiple sets of variables, we will extract all the relevant RRs or ORs.

Progression-free survival: we will extract adjusted and unadjusted OR, HR or RR with 95% confidence intervals.

Time to treatment failure: we will extract adjusted OR, HR or RR with 95% confidence intervals between TTF and the prognostic factor of interest. We will extract all relevant estimated effects when they are adjusted for any additional factors.

Immune-related adverse events: we will extract the univariate unadjusted and adjusted OR or RR with 95% CI of the prognostic factor and the immune-related adverse events**.**

Adverse events of any grade: we will extract the univariate unadjusted and adjusted OR or RR with 95% CI.

For all the above outcomes, when a study reported the estimated effects that are adjusted for different sets of variables, we will extract all the relevant RRs or ORs for each set of variables.

Dealing with missing data

We will contact the authors of the included studies to obtain or clarify key missing data.

When time-to-event analyses have been performed, but adjusted hazard ratio estimates and their uncertainty are unavailable, if the summary statistics reported permit, we will attempt to derive unadjusted estimates and their SEs following guidance described by Tierney and colleagues [31].

Assessment of heterogeneity

We will assess between-study heterogeneity related to two key areas as follows.

- Clinical heterogeneity: we expect there to be clinical heterogeneity between included studies due to varying participant characteristics, such as different stages of cancer, comorbidities and medications, and different treatment regimens (e.g. treatment with chemotherapy alone, immunotherapy alone or the combination of chemotherapy and immunotherapy, and whether it is first or second line of treatment). Clinical heterogeneity may also result from studies using different definitions of increased baseline blood eosinophil levels.
- Methodological heterogeneity: we expect there to be methodological heterogeneity between included studies due to varying study designs, methods of data analysis and risk of bias assessments.

We will explore the impact of these sources of heterogeneity on our meta-analyses. As relying on I^2 statistics alone to quantify heterogeneity can be problematic in certain situations, we will quantify heterogeneity using I^2 statistics, Tau^2 and prediction intervals [32].

Assessment of reporting bias

Reporting bias is likely to be a significant issue in prognostic factor research. Furthermore, it is uncommon for prognostic factor studies to be prospectively registered, which makes it hard to determine whether reporting is adequate [33]. Using the measure of association and its SE, we will create a funnel plot to investigate the possibility of small-study effects. Using the R package metamisc [34], we will test for funnel plot asymmetry and create contour-enhanced funnel plots. Since many of these tests produce insufficient type-I error rates and frequently lack the power to detect asymmetry, we will proceed with caution when interpreting the results [35].

Data synthesis

If we have enough data, we will perform a meta-analysis for adjusted estimates (HR, RR, OR) for OS, PFS, ORR, TTF, risk of occurrence of AEs and, in particular, the risk of occurrence of immune-related adverse events. We will combine studies reporting on eosinophil count at baseline in one meta-analysis. We will pool data from different study designs together. We will also try to combine studies using similar eosinophil count cut-off points in one meta-analysis. If it is not feasible to conduct meta-analysis, we will classify the review outcomes as having a positive association, no association or a negative association with eosinophil count, and we will record the statistical significance of the result.

As mentioned above, we expect the included studies to be clinically and methodologically heterogeneous. This is due to aspects such as using different follow-up times, different cut-offs for eosinophil count and different study designs (retrospective or prospective cohort). Therefore, we will use the random-effects model of meta-analysis to combine data.

We will use Cochrane Review Manager [36] and STATA software [37] for the data analysis.

Subgroup analysis and investigation of heterogeneity

We will investigate heterogeneity by performing both subgroup analysis and meta regression. If the number of included studies is sufficient (more than 10) and there is significant heterogeneity (which we will judge by the prediction interval), we will consider performing meta-regression analysis to explore the possible causes of this heterogeneity.

We plan to conduct the following subgroups where sufficient data are available.

- Participant characteristics: age (< 70 versus > 70 years), ECOG performance status (0 to 1 versus 2 or more), smoking status (active smoker or former smoker versus no smoker), sex (male versus female), PD-L1 (TPS, 0% versus 1 to 50% versus more than 50%)
- Details of treatments received: type of systemic treatment, line of treatment
- Study design: retrospective cohort studies and prospective cohort studies

Sensitivity analysis

For sensitivity analysis, we will exclude studies with a high risk of bias from meta-analysis. We will also conduct sensitivity analysis to compare findings when the analysis includes only studies that reported complete information on HR and precision versus also including those for which we had to calculate HR and precision based on other reported information (as described in the section above on 'Dealing with missing data').

Summary of findings and certainty of the evidence

We will create a summary of findings table (SoF) to present the results of the main outcomes of the review: OS, ORR, PFS, TTF, IRAEs and AEs.

We will use the GRADE approach to rate the certainty of evidence as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* [38] and modified for overall prognosis studies [39]. We will rate the evidence as high, moderate, low or very low certainty as follows [39].

- High: we are very confident that the true prognosis (probability of future events) lies close to that of the estimate.
- Moderate: we are moderately confident that the true prognosis (probability of future events) is likely to be close to the estimate, but there is a possibility that it is substantially different.

- Low: our confidence in the estimate is limited; the true prognosis (probability of future events) may be substantially different from the estimate.
- Very low: we have very little confidence in the estimate; the true prognosis (probability of future events) is likely to be substantially different from the estimate.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD015783.

Supplementary material 1 Search strategies

Supplementary material 2 Pilot test

Supplementary material 3 QUIPS risk of bias tool and the judgement for low risk of bias

ADDITIONAL INFORMATION

Acknowledgements

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Nicole Skoetz, University of Cologne and University Hospital Cologne, Germany
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Liz Bickerdike, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing of main article and production of protocol): Laura MacDonald, Cochrane Central Production Service
- Peer reviewers (provided comments and recommended an editorial decision): Jo Platt, Central Editorial Information Specialist (search), and Rachel Richardson, Cochrane Methods Support Unit (methods). One peer reviewer provided clinical peer review but chose not to be publicly acknowledged.

Contributions of authors

- Conceptualisation: Hugues Sultana (HS), Guillaume Eberst (GE), Virginie Westeel (VW), Cindy Barnig (CB)
- Methodology: HS, Tom De Vos (TDV), Reem S Malouf (RSM), François Calais (FC), Corynne Marchal (CM), GE
- Writing of the protocol: HS, TDV, RSM, FC, CM, GE, VW, CB
- Design of the search strategies: FC

Declarations of interest

- HS declares that he has no conflict of interest.
- TDV declares that he has no conflict of interest.
- RM declares that she has no conflict of interest.
- FC declares that he has no conflict of interest. He is an Information Specialist for the Cochrane Lung Cancer Group but was not involved in the editorial process of this protocol.
- CM declares that she has no conflict of interest. She is the Managing Editor for the Cochrane Lung Cancer Group but was not involved in the editorial process of this protocol.
- GE reports consultancy fees from AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis and Pfizer Canada Inc; all are personal payments.
- VW reports participating in speaker bureaus, scientific committees from Amgen, AstraZeneca, Merck Sharp & Dohme Corporation and Roche. She reports participating in scientific advisory board from Amgen; in speaker bureaus from Bristol-Myers Squibb and Sanofi; in board of experts from Ipsen Biopharmaceuticals Inc. She also reports travel expenses from Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck Sharp & Dohme Corporation, Roche and Sanofi; all are personal payments. VW is the Co-ordinating Editor for the Cochrane Lung Cancer Group but was not involved in the editorial process of this protocol.
- CB reports travel expenses from ALK - Abello, AstraZeneca, Chiesi USA, GlaxosmithKline, Novartis and Sanofi Pasteur; paid to institution and not related to the topic of the review. She has no benefit financially from these payments and has no access to or control of the funds.

Sources of support

Internal sources

- No sources of support provided

External sources

- Institut National du Cancer, France

  Funding (INCa 2022-047)

Registration and protocol

Protocol available via DOI 10.1002/14651858.CD015783

Data, code and other materials

As part of the published Cochrane Review, the following is made available for download for users of the Cochrane Library: full search strategies for each database. Template data extraction forms from Excel are available from the authors on reasonable request.

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ADDITIONAL TABLES

Table 1. QUIPS tools showing the rating for low risk of bias across all domains

Domains	Signalling items	Low risk rating
Study participation (selection bias)	Adequate description of the source of target population	Source of the population cohort with non-small lung cancer (NSLC) clearly described (e.g. number of centres, setting and location)
	Method used to identify problem	The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (e.g. consecutive participants). 1. Place of recruitment clearly described 2. Period of recruitment and follow-up time clearly described
	Inclusion and exclusion criteria	Clear inclusion and exclusion criteria described (e.g. including NSLC stage and treatment)
	Adequate study participation	Sample size calculation to identify that there is adequate participation in the study
	Baseline characteristics	Reporting on key participant characteristics (e.g. sex, smoking status, mutational status, histological subtype)
Study attrition (attrition bias)	Proportion of baseline sample available for analysis	Response rate (proportion of the study sample providing outcome data) is adequate, with a response > 80%.

Table 1. QUIPS tools showing the rating for low risk of bias across all domains *(Continued)*

	Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.
	Reasons for loss to follow-up are described	Reasons for loss to follow-up are described for all dropouts.
	Outcome and prognostic factor information on those lost to follow-up	There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Prognostic factor (PF) measurement (measurement bias)	Definition of the PF	Definition of threshold values for eosinophilia is provided.
	Valid and reliable measurement of PF	The method for measuring eosinophilia is sufficiently valid and reliable.
	Method and setting of PF measurement	The method of measuring eosinophilia is the same for all study participants.
	Proportion of data on PF available for analysis	More than 80% of the study sample has completed data for eosinophilia counts.
	Method used for missing data	Appropriate methods of imputation are used for missing eosinophilia counts data.
Outcome measurement (measurement bias)	Definition of the outcome	A clear definition of the outcome is provided.
	Valid and reliable measurement of outcome	The method of outcome measurement used in valid and reliable to limit misclassification bias.
	Method and setting of outcome measures	The method and setting of outcome measurement is the same for all study participants.
Study confounding (confounder bias)	Important confounders adjusted for	All important confounders are measured (e.g. active asthma, active allergy, active parasitosis).
	Definition of the confounding factor	Clear definitions of the important confounders measured are provided.
	Method and setting of confounding	The method and setting of confounding measurement are the same for all study participants.
	Appropriate accounting for confounders	Important potential confounders are accounted for in the study design (e.g. active asthma, active allergy, active parasitosis).
Statistical analysis and reporting (analysis and reporting bias)	Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.
	Model development strategy	The selected statistical model is adequate for the study design.
	Reporting of results	There is no selective reporting of results.
Overall risk of bias	**High**: most items are answered with 'no' **Low**: all items answered with 'yes' **Moderate**: most items are answered with 'unclear'	

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