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# Do statins improve outcomes for patients with non-small cell lung cancer? A systematic review and meta-analysis protocol

Feng Li,[1,2] Guangyu Liu,[3] Raheleh Roudi,[4] Qi Huang,[5] Marc Swierzy,[1] Mahmoud Ismail,[1] Song Zhao,[2] Jens-Carsten Rueckert[1]

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FL, GL and RR contributed equally.

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For numbered affiliations see end of article.

**Correspondence to**
Professor Jens-Carsten Rueckert;
jens-c.rueckert@charite.de

## ABSTRACT

**Introduction** Lung cancer is the most common neoplasm and the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC), accounting for 85% of all lung cancer cases, is frequently diagnosed at an advanced and metastatic stage. In addition, survival of patients with NSCLC has not improved significantly over the recent decades. Statins are used as a cholesterol-lowering agent, but recently preclinical and clinical studies have revealed their anticancer effects. Thus, this systematic review and meta-analysis aims to clarify whether statins improve the prognosis of patients with NSCLC.

**Methods and analysis** We will search MEDLINE (PubMed), EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov with no restriction on language. Both randomised controlled trials (RCTs) and observational cohort studies evaluating the prognostic role of statins in patients with NSCLC will be included. The primary outcome will be overall survival, and the secondary outcomes will include cancer-specific survival, disease-free survival and cancer recurrence. Two assessors will assess the RCTs using the Cochrane Collaboration's risk of bias tool and the observational cohort studies according to ROBINS-I. Publication bias will be assessed by funnel plot using the STATA software v.13.1.

**Ethics and dissemination** No ethical issues are predicted. This systematic review and meta-analysis aims to describe the prognostic effects of statins in patients with NSCLC, which would help clinicians to optimise treatment for patients with NSCLC. These findings will be published in a peer-reviewed journal and presented at national and international conferences.

**PROSPERO registration number** CRD42016047524.

## Strengths and limitations of this study

- This is the first systematic review aiming to summarise the evidence on whether statins improve the prognosis of patients with non-small cell lung cancer (NSCLC).
- Another strength could be the inclusion of both randomised studies and observational studies.
- This systematic review will be limited to excluding unpublished studies and including studies with the timing of intervention being both before and after the diagnosis of NSCLC.

## INTRODUCTION

Lung cancer is the most common malignant tumour and the leading cause of cancer-related death all over the world.[1] The incidence rate of lung cancer still shows an alarming trend.[2] Clinically, small cell lung cancer and non-small cell lung cancer (NSCLC) are two main subtypes of lung cancer, of which NSCLC accounts for approximately 85% of the cases.[1 3 4] In recent years, although studies have shown survival benefits from low-dose CT screening and tyrosine kinase inhibitors (TKI) specific for epidermal growth factor receptor (EGFR),[5–11] the 5-year lung cancer-specific survival is only 18%.[1] This is partly because most patients are diagnosed at an advanced stage of the disease, and a large proportion of patients with advanced NSCLC are resistant to radiotherapy and chemotherapy, as well as targeted therapy.[1 4] Therefore, there is an urgent requirement to explore new therapies and optimise current treatment to improve the survival of patients with NSCLC.

Statins are inhibitors of 3-hydroxy 3-methylglutaryl-CoA (HMG-CoA) reductase, which is the rate-controlling enzyme in the production of mevalonate.[12] Statins can reduce the plasma cholesterol level, and are the most commonly used drugs for preventing cardiovascular diseases and decreasing mortality and morbidity.[13 14] Mounting evidence has demonstrated that statins are involved in the function of EGFR-related signalling pathways and c-Jun N-terminal kinase pathway.[15] Furthermore, previous studies have indicated that statins exert anticancer effects by

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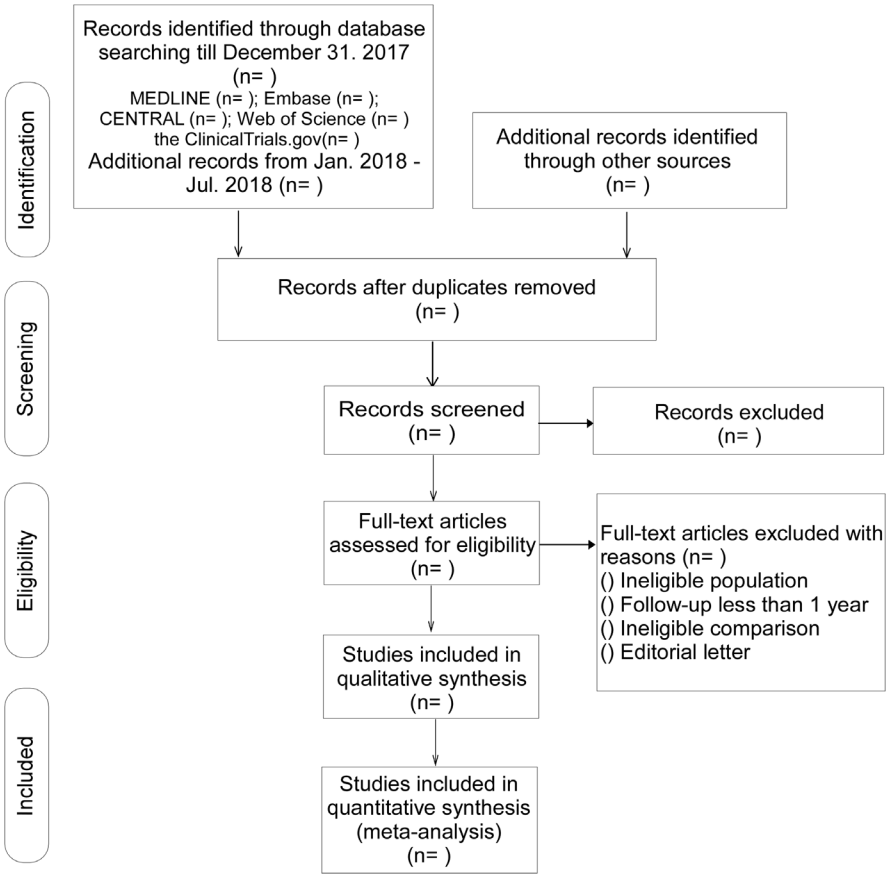



**Figure 1** Flow chart showing identification and screening of eligible studies from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and the ClinicalTrials.gov for inclusion in this systematic review.

inducing apoptosis and inhibiting tumour cell growth and angiogenesis.[16–18] Although it is controversial, many previous clinical publications suggest that statin use is associated with improved survival in patients with NSCLC.[19–21] This systematic review and meta-analysis will explore the effects of statins in patients with NSCLC.

## OBJECTIVES

This systematic review and meta-analysis aims to summarise the existing evidence to determine whether statins change the prognosis of patients with NSCLC. The primary objective is to demonstrate whether statins improve the overall survival of patients with NSCLC. The secondary objectives are to assess whether cancer recurrence, cancer-specific survival and disease-free survival differ between statins-using and non-statins-using patients with NSCLC.

## METHODS

This systematic review has been developed in accordance with the guidelines detailed on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist,[22] and the protocol is reported according to its extension for protocols (PRISMA-P 2015).[23 24] In addition, the flow chart (figure 1) will be employed in describing the study identification and selection process. The protocol of this systematic review has been registered in PROSPERO (trial registration number: CRD42016047524).

## INCLUSION CRITERIA

### Type of studies

We will include both randomised controlled trials (RCTs) and observational cohort studies. Studies assessing cell lines and animal models only, review articles, proceedings, conferences and case–control studies will be excluded.

### Type of participants

We will include all patients of both genders who are diagnosed with NSCLC. Tumour classification will be made according to the 2011 WHO classification.[25]

### Type of intervention

The intervention will be use of statins, which means patients who have taken statins at any type or dose before or after the diagnosis will be included in the treatment group.

### Type of control

The control group will be patients who have been allocated to the control group during the study, which means



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the comparators given can be either placebos or no treatment of statins.

### Type of outcomes

The primary outcome will be overall survival of patients with NSCLC. The secondary outcomes will include cancer recurrence, cancer-specific survival and disease-free survival.

## SEARCH STRATEGY

We will search the following databases: MEDLINE (PubMed), EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials and the ClinicalTrials.gov, until 31 July 2018.

### PubMed search strategy

The details of the PubMed database search strategy and syntax are sequentially provided in online supplementary appendix 1.

### Other resources

The reference lists of the relevant original studies will be searched for additional studies, as well as reviews and key journals, such as *'Lung Cancer'* (until 31 July 2018), *'Clinical Lung Cancer'* (until 31 July 2018), *'Clinical Cancer Research'* (until 31 July 2018), *'Journal of Clinical Oncology'* (until 31 July 2018), *'JAMA'* (until 31 July 2018), *'Lancet'* (until 31 July 2018) and *'the New England Journal of Medicine'* (until 31 July 2018). The hand-searching approach will be a manual page-by-page examination of all the issues.

There will be no restrictions on language or publication year. Studies written in languages other than English will be translated with the help of international scientists in our institutes. In addition, we will exclude unpublished studies.

### Data collection and analysis

#### Selection of studies

Two reviewers will independently screen the titles and abstracts of all studies identified from the databases according to the inclusion criteria. Subsequently, the full texts of the identified studies will be reassessed independently by the two reviewers, verifying the reasons for inclusion and exclusion. Disagreements will be resolved by consulting a third reviewer.

#### Data extraction

A data extraction form will be developed, and the study data will be independently assessed and extracted by two reviewers. The following data will be extracted from all the included studies:

1. Study characteristics (author, year of publication, study design, setting, locations and patient enrolment strategies, and sample size).
2. Participants' characteristics (age, gender, ethnicity, smoking status, alcohol consumption, histopathological diagnosis, tumour, node, metastases (TNM) stage, history of treatment, associated comorbidities, timing of administration of statins, type of statins, dose of statins, comparator given and follow-up period).

If the reported data are not sufficient, we will contact the authors for further information. We will also pay extra attention to the confounding factors in the retrospective observational cohort studies.

#### Assessment of methodological quality

Two assessors will assess the methodological quality of RCTs using the Cochrane Collaboration's risk of bias tool[26] and observational studies according to The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I).[27] ROBINS-I is a new tool to assess risk of bias in non-randomised studies of interventions. ROBINS-I has seven domains of bias, including bias due to confounding, selection of participants, interventions themselves, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result. We have identified the following confounders: TNM stage and history of treatment (including chemotherapy, radiotherapy, targeted therapy and surgical therapy), which are important for the survival of patients with NSCLC. The reviewers should respond to the questions on signalling to judge the risk of bias in each domain, finally acquiring an overall risk of bias judgement for the outcome being assessed. Disagreements will be resolved by consulting a third independent reviewer.

#### Measures of treatment effect

The HR will be used to summarise survival data and dichotomous data, respectively, along with 95% CI. If an HR is not presented in an eligible study, for example only an OR or relative risk (RR) is available, we will estimate the HR using the information available in the study according to the methods reported in the previous studies.[28 29] Because if there are sufficient data to estimate an OR or RR, then there are usually sufficient data to estimate an HR. Also, if multiple effect estimates are presented in a paper, we will extract the result adjusted for the greatest number of our prespecified confounders.[30]

#### Addressing missing data

Missing relevant data will be excluded from analysis only after contacting the author but failing to acquire them. Sensitivity analysis will be conducted to explore if these missing data will influence the results of the meta-analysis.

#### Assessment of heterogeneity

Heterogeneity among studies will be measured using the Cochran Q test ($\chi^2$) and $I^2$ test. We will interpret it using the following guide: $I^2$, 0%–25% suggesting low heterogeneity, 25%–50% moderate heterogeneity and 75%–100% high heterogeneity.

#### Assessment of reporting bias

Since detecting and overcoming publication bias are problematic and firm guidance is not yet offered, we will



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use funnel plot to assess reporting bias, with results being interpreted cautiously.

### Strategy for data synthesis

Extracted data will be entered into Review Manager V.5.3 software for aggregating risk estimates (HR and 95% CI) by the first researcher and independently checked by the second one. We will use fixed-effect or random-effects methods as appropriate for analysis. If heterogeneity among the studies is identified as considerable, we will apply the random-effects method for analysis.

### Subgroup analyses

Subgroup analyses are planned as follows:

1. Associated comorbidity such as hyperlipidaemia, coronary heart disease and so on.
2. Disease stage.
3. Cancer subtype.
4. Treatment type: surgery, chemotherapy and radiotherapy.
5. The time points at which patients start to take statins: prediagnosis or postdiagnosis.
6. Study type: RCT and retrospective studies.
7. Comparator given: placebo or no treatment.

### Sensitivity analysis

A sensitivity analysis will be conducted to test the impact of the results with respect to the methodological quality items rated by the ROBINS-I and the Cochrane tool. Meta-analyses will be repeated after excluding studies with lower methodological quality and studies with high or unclear risk of bias. To evaluate the stability of the results, we will also conduct the leave-one-out sensitivity analysis. Sensitivity analyses will be reported with a summary table, and reviewed conclusions will be interpreted by making comparisons between the two meta-analyses.

## Confidence in cumulative evidence

The quality of the evidence will be assessed using the scoring system of the Grading of Recommendations Assessment, Development and Evaluation Working Group. According to the final score, which will be acquired by summarising the score of each item in the scoring system, the quality of evidence is categorised into four levels: high (≥4 points), moderate (3 points), low (2 points) and very low (≤1 point).[31]

## Patient and public involvement

Patients and the public were not involved in this study.

## DISCUSSION

Lung cancer, especially NSCLC, is among the most common cancers for both men and women. Although many patients with NSCLC using EGFR-TKIs have achieved encouraging results, there are still a large proportion of patients who cannot benefit from them. Statins, considered as safe, cheap and effective drugs, are commonly used in the primary and secondary prevention of cardiovascular diseases; however, some preclinical and clinical studies have shed light on their anticancer effects and repurposed them as promising anticancer agents.

Our systematic review will clarify the prognostic effect of statins in patients with NSCLC, which would help patients and clinicians to optimise the treatment of NSCLC, especially patients with coexisting cardiovascular disease. This systematic review may also help guideline developers in the management of patients with NSCLC.

## ETHICS AND DISSEMINATION

No ethical issues are predicted. This systematic review and meta-analysis will describe the prognostic effects of statins in patients with NSCLC, which would help clinicians to optimise the treatment for patients with NSCLC. These findings will be published in a peer-reviewed journal and presented at national and international conferences.

**Author affiliations**
[1]Department of General, Visceral, Vascular and Thoracic Surgery, Charite Universitatsmedizin Berlin, Berlin, Germany
[2]Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, Henan, China
[3]Department of Anesthesiology, Peking University First Hospital, Beijing, China
[4]Department of Oncopathology, Research Center, Iran University of Medical Sciences, Tehran, Iran
[5]Department of Thoracic Surgery, Peking University People's Hospital, Beijing, China

**Contributors** FL and GL came up with the original idea of this work. QH assisted in protocol design. MS, MI, SZ and J-CR provided valuable advice for the research protocol. RR, FL and GL drafted the protocol, which was revised by all the authors. GL and FL will search for studies, extract and analyse the data, and QH will be consulted if they do not reach an agreement.

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