Prognostic factors for chronic post-surgical pain after lung or pleural surgery: A protocol for a systematic review and meta-analysis

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BMJ Open  Prognostic factors for chronic postsurgical pain after lung or pleural surgery: a protocol for a systematic review and meta-analysis

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Introduction Chronic post-surgical pain (CPSP) after lung or pleural surgery is a common complication and associated with a decrease in quality of life, long-term use of pain medication and substantial economic costs. An abundant number of primary prognostic factor studies are published each year, but findings are often inconsistent, methods heterogeneous and the methodological quality questionable. Systematic reviews and meta-analyses are therefore needed to summarise the evidence.

Methods and analysis The reporting of this protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist. We will include retrospective and prospective studies with a follow-up of at least 3 months reporting patient-related factors and surgery-related factors for any adult population. Randomised controlled trials will be included if they report on prognostic factors for CPSP after lung or pleural surgery. We will exclude case series, case reports, literature reviews, studies that do not report results for lung or pleural surgery separately and studies that modified the treatment or prognostic factor based on pain during the observation period. MEDLINE, Scopus, Web of Science, Embase, Cochrane, CINAHL, Google Scholar and relevant literature reviews will be searched. Independent pairs of two reviewers will assess studies in two stages based on the PICOTS criteria. We will use the Quality in Prognostic Studies tool for the quality assessment and the CHARMS-PF checklist for the data extraction of the included studies. The analyses will all be conducted separately for each identified prognostic factor. We will analyse adjusted and unadjusted estimated measures separately. When possible, evidence will be summarised with a meta-analysis and otherwise narratively. We will quantify heterogeneity by calculating the Q and I² statistics. The heterogeneity will be further explored with meta-regression and subgroup analyses based on clinical knowledge. The quality of the evidence obtained will be evaluated according to the Grades of Recommendation Assessment, Development and Evaluation guideline 28. Ethical and dissemination Ethical approval will not be necessary, as all data are already in the public domain. Results will be published in a peer-reviewed scientific journal.

PROSPERO registration number CRD42021227888.

Strengths and limitations of this study

- This systematic review and meta-analysis will be the first to systematically identify all prognostic factors for chronic postsurgical pain after lung or pleural surgery and to summarise the evidence.
- To ensure methodological quality, this systematic review and meta-analysis will be conducted following the PROGnosis RESEARCH Strategy guide for prognostic factor meta-analyses.
- Heterogeneity in the methods, the study populations and the reported outcomes of the included studies together with unexplained heterogeneity, will result in some level of uncertainty in our conclusions.

INTRODUCTION

Lung or pleural surgery is performed for a variety of diseases or injuries, such as lung cancer, cancer of the pleura, lung emphysema, lung transplantation and abscess after trauma or pleurodesis for recurrent pneumothoraces. The thorax can be surgically accessed with a regular thoracotomy or with less invasive video-assisted thoracic surgery (VATS). Thoracic surgery is associated with chronic post-surgical pain (CPSP), which is classified as any pain related to the surgery and persisting for 3 months or longer after surgery.1,2 CPSP often starts as a hard to control and acute post-surgical pain which later transitions into a persisting chronic pain.3 The pain is regularly localised at the chest wall and related to the area of surgery, but it can also be referred to a different area. It commonly increases with movement and often has a neuropathic component.4,5 CPSP has been observed in as many as 57% and 47% of the patients 3 and 6 months after thoracic surgery, respectively.6 Hence, thoracic surgery has the highest incidence of CPSP among all types of surgery.7 VATS is assumed...
Objective factors evidence as a narrative, as appropriate.

**METHODS AND ANALYSIS**

The reporting of this protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist. It has been registered at the International Prospective Register of Systematic Reviews. For the project design we used guidance from the PROGnosis RESearch Strategy group, and specifically the guide for systematic reviews and meta-analyses for prognostic factor studies. The results of the systematic review will be reported following the PRISMA checklist.

**Study eligibility**

We will include retrospective and prospective studies naming and evaluating a prognostic factor relating to chronic pain following lung or pleural surgery with at least 3 months of follow-up. Randomised controlled trials will be included if they report on prognostic factors for chronic pain after lung or pleural surgery. Case series, case studies, literature reviews, studies that do not report results for lung or pleural surgery separately and studies that modified the treatment or prognostic factor based on pain during the observation period will be excluded. We will use the PICOTS system as selection criteria for studies with the appropriate study type. (Table 1). The PICOTS system is an updated modification for prognostic studies of the traditional PICO system, incorporating ‘timing (T)’ and ‘setting (S)’. Timing includes at what time points the prognostic factors are being measured and appraised. The PICOTS system is an updated modification for prognostic studies of the traditional PICO system, incorporating ‘timing (T)’ and ‘setting (S)’.

**Search strategy**

We will search key health and medical databases (MEDLINE, Scopus, Web of Science, Embase, Cochrane, CINAHL and Google Scholar) for peer-reviewed literature.
from inception of each database until most-recent available study on the date of conducting our final search. Screening of studies will start as soon as possible, and we aim that the last search date will not be longer than 12 months from the publication date of the final review. The systematic search will be built by an experienced information scientist and will be adapted to fit each information source. The reporting and retrieval of prognostic factors is generally known to be poor, with no specialised filters available. Hence a broad search will be employed using the most recent prognostic strategies, offering a high sensitivity at the cost of a lower specificity. We will use no restrictions on language, study status or time of publication. If translation is necessary, we will ask a colleague who is fluent in that language to translate. When this is not possible, we will use the Cochrane task exchange service or Google Translate. The search strategy is included in online supplemental file 1, with the adaptations for each database. Because of potential limitations of the electronic search strategy, we will supplement our search with reference searches of relevant literature studies.

Study screening
Independent pairs of two reviewers will assess studies in two stages based on the inclusion and exclusion criteria. They will screen studies in stage one on title and abstract and in stage two on the full text. Differences will be resolved through either a consensus meeting or consultation of a third reviewer in both selection phases. We will use the PRISMA flowchart to display the study selection process, including the exclusion reasons of non-eligible studies. Studies retrieved from the searches will be stored and screened in EndNote V.X.9. The excluded studies will be stored in EndNote subgroups for each exclusion reason. The data that will be extracted from eligible studies will be stored and managed in Microsoft Excel V.16.43.

Data extraction
For the data collection process we will use the standardised CHARMS-PF checklist, which is based on the CHARMS checklist, but adjusted for prognostic factor studies. It has nine domains, covering everything needed to reliably pool data: source of data, participants, outcomes to be predicted, prognostic factors, sample size, missing data, analysis, results and interpretation and discussion. Specific attention will be paid to the following data items: Reported factors of prognostic interest, definition and measurement of outcomes, adjusted and unadjusted outcomes, adjustment factors, regression methods and timing. When multiple follow-up time points are available, we will use a time point of at least 3 months that is closest to 3 months. If only the mean follow-up or the range of follow-up is reported, it needs to be at least 3 months. Any additional information deemed necessary will be added in a bespoke Excel data extraction file. If information in a study is missing or unclear, the primary study authors will be contacted with the request to provide additional information. We will consider the study with the biggest sample size or the most recent, as appropriate, as the most relevant one when there are multiple publications with the same or overlapping participant data.

Risk of bias in individual studies
The quality of included studies will be assessed by two independent reviewers with the Quality in Prognostic Studies tool. This tool contains six domains: Study participation, study attrition, prognostic factor measurement, outcome measurement, study covariates and statistical analysis and reporting. Each domain is rated as low, moderate or high risk of bias. If information in a study is missing or unclear, the authors will be contacted with the request to provide additional information. Differences between the two reviewers will be resolved through either a consensus meeting or consultation of a third reviewer.

Data synthesis
The characteristics of the identified prognostic factors will be summarised in a table. For the quantitative synthesis we will obtain ORs, risk ratios (RRs) and HRs as measures of association as reported in each included study. The mean difference will also be considered as an appropriate measure of association for continuous prognostic factors. Adjusted and unadjusted estimates for each factor will be considered and analysed separately. The OR, RR and HR will also be considered separately. A meta-analysis will be performed for each prognostic factor when reported by at least five studies with similar measures of association. In cases where either the measure (OR, RR or HR), or its SE are not reported, where possible we will estimate them from any available data in the included study, such as confidence intervals, Kaplan-Meier curves, logrank test p values or other as appropriate. We will explore any differences between the reported and estimated measures through a sensitivity analysis. We will also include a sensitivity analysis when there is heterogeneity between studies in how chronic pain is defined. For pooling the data, we will use the DerSimonian and Laird random effects model to account for expected between study heterogeneity. We will perform a univariate meta-regression for each continuous prognostic factor reported by 10 or more studies. All analyses will be performed with the metafor package in the latest version of R and RStudio. When quantitative synthesis is not possible, we will summarise the evidence narratively.

Subgroup analyses
We will perform subgroup analyses where possible to further explore the heterogeneity. Based on clinical knowledge, the following subgroups will be investigated: Malignant diseases, regional anaesthesia (particularly
intercostal infiltration, single shot and continuous blocks and duration), neuropathic pain and surgical technique (particularly VATS or no VATS).

**Publication bias**

Funnel plots will be used to assess potential publication bias for factors of prognostic interest that are reported by 10 or more studies. Funnel plots suffer from low power and this is more problematic for observational studies (as are studies of prognosis) where there is additionally increased heterogeneity. To statistically test the asymmetry of the funnel plots we will use the Harbord test, and any findings will be interpreted with caution.

**Rating of evidence**

The evidence and inferences will be evaluated according to the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) guidelines (GRADE guideline 28) for assessing the evidence from prognostic factors. It contains five domains: Risk of bias, inconsistency, imprecision, indirectness and publication bias.

**Contributors**

PRDC designed and wrote the protocol in close collaboration with SEH. MH and PMS provided the idea of the topic. MT and SEH contributed to the design of the statistical methods. CSG contributed to finding the a priori prognostic factor. MH and MK coordinated the whole process. All authors read, provided feedback and approved the final manuscript.

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**Competing interests**

None declared.

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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**REFERENCES**


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Supplement 1

Embase

('chronic pain'/exp OR (((chronic* OR constant* OR continu* OR persist* OR longterm OR long-term OR
longstanding OR long-standing OR longlasting OR long-lasting OR phantom) NEAR/6 (pain* OR
discomfort* OR complaint*)):ti,ab,kw)) AND ('postoperative pain'/exp OR (((postoperative OR
posttreatment OR postsurg*) NEAR/6 (pain* OR analgesi*)) OR ((post OR after OR follow*) NEAR/3
(surg* OR operat* OR treat* OR resect* OR transplant*) NEAR/6 (pain* OR analgesi*)) OR ((post*
NEAR/1 pain*)) OR pain-relief-after OR ((post-extraction OR postextraction OR amputat* OR
mediastinoscopy OR sternotomy OR thoracoplasty OR thoracoscopy OR thoracotomy OR thoracotomy
OR thoracocentesis OR thymectomy OR tracheotomy OR tracheotomy OR bronchoscopy OR
pneumonolysis OR pneumonectomy OR esophagectomy OR oesophagectomy OR postmediastinoscop*
OR poststernotomy* OR postthoracoplast* OR postthoracostom* OR postthoracotomy* OR
postthoracocentesis OR postthymectom* OR posttracheostom* OR
posttracheotom* OR postbronchoscop* OR postpneumonolysis OR postpneumonectomy* OR
postesophagectom* OR postoesophagectom* OR postlucoplast*) NEAR/6 (pain* OR discomfort OR
analgesi*)):ti,ab,kw) AND ('thorax surgery'/exp NOT 'heart surgery'/exp) OR 'lung tumor'/exp
OR 'lungs'/exp OR ('lung OR pulmonary OR esophag* OR oesophag* OR trachea* OR rib OR thym* OR chest
OR pleura*) NEAR/6 (surg* OR operat* OR resect*) OR mediastinoscop* OR sternotomy* OR
thoracoplast* OR thoracoscopy* OR thoracostom* OR thoracotomy* OR thoracocentesis OR thymectomy*
OR tracheostomy* OR tracheotom* OR bronchoscopy* OR pneumonolysis OR pneumonectomy* OR
esophagectomy* OR oesophagectomy* OR lobectom* OR postmediastinoscop* OR poststernotomy* OR
postthoracoplast* OR postthoracostom* OR postthoracotomy* OR postthoracocentesis OR postthymectom*
OR postthoracotomy* OR posttracheostom* OR posttracheotomy* OR postbronchoscop* OR postpneumonolysis
OR postpneumonectomy* OR postesophagectom* OR postoesophagectom* OR ((lung OR pulmonary OR thym*)
NEAR/6 (transplant* OR graft*)) OR ((esophag* OR oesophag*) NEAR/6 (anastom* OR transect* OR dilat* OR
reconstruct*)):ti,ab,kw) NOT [conference abstract]/lim NOT [(animals)/lim NOT [humans]/lim]

Medline

(Chronic Pain/ OR (((chronic* OR constant* OR continu* OR persist* OR longterm OR long-term OR
longstanding OR long-standing OR longlasting OR long-lasting OR phantom) ADJ6 (pain* OR discomfort*
OR complaint*)):ti,ab,kf)) AND (Pain, Postoperative/ OR (((postoperative OR posttreatment OR
postsurg*) ADJ6 (pain* OR analgesi*)) OR ((post OR after OR follow*) ADJ3 (surg* OR operat* OR treat*
OR resect* OR transplant*) ADJ6 (pain* OR analgesi*)) OR ((post* ADJ1 pain*)) OR pain-relief-after OR
((post-extraction OR postextraction OR amputat* OR mediastinoscopy OR sternotomy OR thoracoplasty
OR thoracotomy OR thoracocentesis OR thymectomy OR tracheotomy OR bronchoscopy OR
pneumonolysis OR pneumonectomy OR esophagectomy OR oesophagectomy OR postmediastinoscop*
OR poststernotomy* OR postthoracoplast* OR postthoracostom* OR postthoracotomy* OR
postthoracocentesis OR postthymectom* OR posttracheostom* OR posttracheotomy* OR postbronchoscop*
OR postpneumonolysis OR postpneumonectomy* OR postesophagectom* OR postoesophagectom* OR
postlucoplast*) ADJ6 (pain* OR discomfort OR analgesi*)):ti,ab,kf) AND
(Thoracic Surgery/ OR (exp Thoracic Surgical Procedures/ NOT exp Cardiac Surgical Procedures/ ) OR
OR tracheostomy OR tracheotomy OR bronchoscopy OR pneumonolysis OR pneumonectomy OR esophagectomy OR oesophagectomy OR postmediastinoscop* OR poststernotom* OR postthoracoplast* OR postthoracoscop* OR postthoracostom* OR postthoracotom* OR postthoracocentesis OR postthymectom* OR posttracheostom* OR posttracheotom* OR postbronchoscop* OR postpneumonolysis OR postpneumonectom* OR postesophagectom* OR postoesophagectom* OR postlobectom*) NEAR/6 (pain* OR discomfort OR analgesi*))):ti,ab) AND (((thora* OR lung OR pulmonary OR esophag* OR oesophag* OR trachea* OR rib OR thym* OR chest OR pleura*) NEAR/6 (surg* OR operat* OR resect*)) OR mediastinoscop* OR sternotom* OR thoracoplast* OR thoracoscop* OR thoracostom* OR thoracotom* OR thoracocentesis OR thymectom* OR tracheostom* OR tracheotom* OR bronchoscop* OR pneumonolysis OR pneumonectom* OR esophagectom* OR oesophagectom* OR lobectom*) OR postmediastinoscop* OR poststernotom* OR postthoracoplast* OR postthoracoscop* OR postthoracostom* OR postthoracotom* OR postthoracocentesis OR postthymectom* OR posttracheostom* OR posttracheotom* OR postbronchoscop* OR postpneumonolysis OR postpneumonectom* OR postesophagectom* OR postoesophagectom* OR postlobectom*) OR ((lung OR pulmonary OR thym*) NEAR/6 (transplant* OR graft*)) OR ((esophag* OR oesophag*) NEAR/6 (anastom* OR transect* OR dilat* OR reconstruct*)):ti,ab)

CINAHL
(MH Chronic Pain OR TI (((chronic* OR constant* OR continu* OR persist* OR longterm OR long-term OR long-standing OR long-lasting OR long lasting OR phantom) NS (pain* OR discomfort* OR complaint*)) OR AB (((chronic* OR constant* OR continu* OR persist* OR longterm OR long-term OR long-standing OR long-lasting OR long-lasting OR phantom) NS (pain* OR discomfort* OR complaint*)))) AND (MH Postoperative Pain OR TI (((postoperative OR posttreatment OR postsurg*) NS (pain* OR analgesi*)) OR ((post OR after OR follow*) N2 (surg* OR operat* OR treat* OR resect* OR transplant*) NS (pain* OR analgesi*)) OR ((post* N1 pain*)) OR pain-relief-after OR ((post-extraction OR postextraction OR amputat* OR mediastinoscopy OR sternotomy OR thoracoplasty OR thoracotomy OR thoracectomy OR thoracostomy OR thoracoscop* OR thoracoplast* OR poststernotom* OR postthoracoplast* OR postthoracoscop* OR postthoracostom* OR postthoracotom* OR postthoracocentesis OR postthymectom* OR posttracheostom* OR posttracheotom* OR postbronchoscop* OR postpneumonolysis OR postpneumonectom* OR postesophagectom* OR postoesophagectom* OR postlobectom*) NS (pain* OR discomfort OR analgesi*)) OR ((lung OR pulmonary OR thym*) NEAR/6 (transplant* OR graft*)) OR ((esophag* OR oesophag*) NEAR/6 (anastom* OR transect* OR dilat* OR reconstruct*)):ti,ab)

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OR pleura*) N5 (surg* OR operat* OR resect*)) OR mediastinoscop* OR sternotom* OR thoracoplast* OR thoracoscop* OR thoracostom* OR thoracotom* OR thoracocentesis OR thymectom* OR tracheostom* OR tracheotom* OR bronchoscop* OR pneumonolysis OR pneumonectom* OR esophagectom* OR oesophagectom* OR lobectom* OR postmediastinoscop* OR poststernotom* OR postthoracoplast* OR postthoracoscop* OR postthoracostom* OR postthoracotom* OR postthoracocentesis OR postthymectom* OR posttracheostom* OR posttracheotom* OR postbronchoscop* OR postpneumonolysis OR postpneumonectom* OR postesophagectom* OR postoesophagectom* OR postlobectom* OR ((lung OR pulmonary OR thym*) N5 (transplant* OR graft*)) OR ((esophag* OR oesophag*) N5 (anastom* OR transect* OR dilat* OR reconstruct*)) OR AB(((thora* OR lung OR pulmonary OR esophag* OR oesophag* OR trachea* OR rib OR thym* OR chest OR pleura*) N5 (surg* OR operat* OR resect*)) OR mediastinoscop* OR sternotom* OR thoracoplast* OR thoracoscop* OR thoracostom* OR thoracotom* OR thoracocentesis OR thymectom* OR tracheostom* OR tracheotom* OR bronchoscop* OR pneumonolysis OR pneumonectom* OR esophagectom* OR oesophagectom* OR lobectom* OR postmediastinoscop* OR poststernotom* OR postthoracoplast* OR postthoracoscop* OR postthoracostom* OR postthoracotom* OR postthoracocentesis OR postthymectom* OR posttracheostom* OR posttracheotom* OR postbronchoscop* OR postpneumonolysis OR postpneumonectom* OR postesophagectom* OR postoesophagectom* OR postlobectom* OR ((lung OR pulmonary OR thym*) N5 (transplant* OR graft*)) OR ((esophag* OR oesophag*) N5 (anastom* OR transect* OR dilat* OR reconstruct*)))) NOT (MH animals+ NOT MH humans)

Scopus
TITLE-ABS-KEY((((chronic* OR constant* OR continu* OR persist* OR longterm OR long-term OR longstanding OR long-standing OR longlasting OR long-lasting OR phantom) W/5 (pain* OR discomfort* OR complaint*))))) AND ((((postoperative OR posttreatment OR postsurg*) W/5 (pain* OR analgesi*)) OR ((post OR after OR follow*) W/2 (surg* OR operat* OR treat* OR resect* OR transplant*) W/5 (pain* OR analgesi*)) OR ((post* W/1 pain*)) OR pain-relief-after OR ((post-extraction OR postextraction OR amputat* OR mediastinoscopy OR sternotomy OR thoracoplasty OR thoracoscopy OR thoracotomy OR thoracostomy OR thoracocentesis OR thymectomy OR tracheostomy OR tracheotomy OR bronchoscopy OR pneumonolysis OR pneumonectomy OR esophagectomy OR oesophagectomy OR postmediastinoscop* OR poststernotom* OR postthoracoplast* OR postthoracoscop* OR postthoracostom* OR postthoracotom* OR postthoracocentesis OR postthymectom* OR posttracheostom* OR posttracheotom* OR postbronchoscop* OR postpneumonolysis OR postpneumonectom* OR postesophagectom* OR postoesophagectom* OR postlobectom* OR ((lung OR pulmonary OR thym*) N5 (transplant* OR graft*)) OR ((esophag* OR oesophag*) N5 (anastom* OR transect* OR dilat* OR reconstruct*))))))
Google scholar
"chronic|constant|persisting|longterm|longstanding|longlasting|phantom pain"
"postoperative|postsurgical pain" "thorax|thoracic surgery|operation"