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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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ABSTRACT

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 I^2 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.

Ethics 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.

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Strengths and limitations of this study

- This systematic review and meta-analysis will be the first to systematically identify all prognostic factors for chronic post-surgical 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 pneumothorces. 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.[3 7] VATS is assumed

to be less painful compared with a regular thoracotomy because it is less invasive, however, incidence and severity of CPSP have been reported to be similar.[8] CPSP after thoracic surgery has been associated with a lower overall quality of life,[9–13] and chronic pain is associated with an increased utilisation of healthcare, increased absenteeism and decreased work-related effectiveness.[14–16] The direct health-related costs of chronic pain have been reported to be US$11 846 annually,[17] and the indirect work-related costs have been reported to be US$29 617 annually.[17] The burden of CPSP for cancer survivors is also increasingly recognised, given the progress that has been made in cancer treatment.[18] Furthermore, CPSP often results in the long-term use of pain medication, particularly opioids, which contributes to overuse, misuse and addiction of opioids,[19–21] and thoracic surgery as an independent factor has also been associated with prolonged postoperative opioid use.[22] Thus, CPSP has significant health and economic related consequences and is a problematic complication. Evidence for prognostic factors can contribute to improved clinical decision-making and individualised risk prediction by healthcare providers. A prognostic factor is defined as any variable affecting the risk of a particular health outcome and should be evaluated in a representative sample of patients assembled at the same time point in the course of their disease.[23 24] It can also contribute to the development of treatment strategies by identifying modifiable prognostic factors as targets.[25] This systematic review and meta-analysis will focus on all relevant reported prognostic factors for CPSP after lung or pleural surgery. There are two main categories we are interested in: Patient-related factors and surgery-related factors. A great number of primary prognostic factor studies are being published each year, however, they are often methodologically poor, their findings inconsistent and the methods heterogeneous.[23] Therefore, systematic reviews and meta-analyses are needed to summarise the evidence.[23 26] Other systematic reviews have been done regarding the incidence, severity and therapeutic interventions of chronic pain after thoracic surgery.[6 27 28] Another review has been done regarding the pathogenic mechanisms and strategies for prevention of chronic pain after thoracotomy.[29] To our knowledge, a systematic review and meta-analysis regarding prognostic factors for CPSP after lung or pleural surgery has not yet been performed.

OBJECTIVES

Our main goal is to carry out a systematic overview of the evidence regarding prognostic factors for CPSP after lung or pleural surgery. Our objectives are to identify, describe and appraise all studies reporting prognostic factors for CPSP after lung or pleural surgery, and summarise the evidence for each prognostic factor, either quantitatively with a meta-analysis or qualitatively by describing the evidence as a narrative, as appropriate.

Table 1 Summary table of the PICOTS used as selection criteria

Population	Any population of adult participants (18 years or older) who have had any type of lung or pleural surgery.
Index prognostic factors	Pre-identified prognostic factors: Preoperative pain, postoperative pain, pain catastrophising score, age, gender, body mass index, diabetes mellitus, exercise tolerance, malignant diseases, chemotherapy, radiation therapy, surgery duration, anaesthesia technique and surgical technique. Any newly identified prognostic factors will also be considered.
Comparator prognostic factors	Because we will systematically identify all prognostic factors and summarise the evidence, no comparator prognostic factors are involved.
Outcome	Chronic post-surgical pain as outcome.
Timing	Follow-up of 3 months or more.
Setting	Any healthcare setting.

METHODS AND ANALYSIS

The reporting of this protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.[30 31] 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.[26] The results of the systematic review will be reported following the PRISMA checklist.[32]

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)'.[33 34] Timing includes at what time points the prognostic factors are being measured and setting includes the intended setting, such as primary or secondary care.[26]

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.[35] 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.[36] 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.[37] 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.[32] Studies retrieved from the searches will be stored and screened in EndNote V.X9.[38] 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,[26] which is based on the CHARMS checklist,[34] 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.[39] 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.[26 40] 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.[41–44] 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.[45 46] We will include a 95% prediction interval in addition to the 95% CI for the pooled measures.[46] Heterogeneity between studies will be assessed for each meta-analysis by visually inspecting forest plots and by calculating the Q statistic and the I^2 statistic.[47] We will perform a univariable 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.[48] 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,[49] 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.[50] 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 factors. MH and MK coordinated the whole process. All authors read, provided feedback and approved the final manuscript.

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REFERENCES

1 Schug SA, Lavand'homme P, Barke A, *et al*. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain* 2019;160:45–52.
2 Treede R-D, Rief W, Barke A, *et al*. A classification of chronic pain for ICD-11. *Pain* 2015;156:1003–7.
3 Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet* 2019;393:1537–46.
4 Guastella V, Mick G, Soriano C, *et al*. A prospective study of neuropathic pain induced by thoracotomy: incidence, clinical description, and diagnosis. *Pain* 2011;152:74–81.
5 Haroutiunian S, Nikolajsen L, Finnerup NB, *et al*. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013;154:95–102.
6 Bayman EO, Brennan TJ. Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: meta-analysis. *J Pain* 2014;15:887–97.
7 Cregg R, Anwar S, Farquhar-Smith P. Persistent postsurgical pain. *Curr Opin Support Palliat Care* 2013;7:144–52.
8 Bayman EO, Parekh KR, Keech J, *et al*. A prospective study of chronic pain after thoracic surgery. *Anesthesiology* 2017;126:938–51.
9 Kinney MAO, Hooten WM, Cassivi SD, *et al*. Chronic postthoracotomy pain and health-related quality of life. *Ann Thorac Surg* 2012;93:1242–7.
10 Kar P, Sudheshna KD, Padmaja D, *et al*. Chronic pain following thoracotomy for lung surgeries: It's risk factors, prevalence, and impact on quality of life - A retrospective study. *Indian J Anaesth* 2019;63:368–74.
11 Peng Z, Li H, Zhang C, *et al*. A retrospective study of chronic postsurgical pain following thoracic surgery: prevalence, risk factors, incidence of neuropathic component, and impact on qualify of life. *PLoS One* 2014;9:e90014.
12 Fiorelli S, Cioffi L, Menna C, *et al*. Chronic pain after lung resection: risk factors, neuropathic pain, and quality of life. *J Pain Symptom Manage* 2020;60:326–35.
13 Loxe SC, de Mello LS, Camara L, *et al*. Chronic pain after lung transplantation and its impact on quality of life: a 4-year follow-up. *Transplant Proc* 2020;52:1388–93.
14 Blyth FM, March LM, Brnabic AJM, *et al*. Chronic pain and frequent use of health care. *Pain* 2004;111:51–8.
15 Blyth FM, March LM, Nicholas MK, *et al*. Chronic pain, work performance and litigation. *Pain* 2003;103:41–7.
16 van Leeuwen MT, Blyth FM, March LM, *et al*. Chronic pain and reduced work effectiveness: the hidden cost to Australian employers. *Eur J Pain* 2006;10:161–6.
17 Parsons B, Schaefer C, Mann R, *et al*. Economic and humanistic burden of post-trauma and post-surgical neuropathic pain among adults in the United States. *J Pain Res* 2013;6:459–69.
18 Brown MR, Ramirez JD, Farquhar-Smith P. Pain in cancer survivors. *Br J Pain* 2014;8:139–53.
19 Huang A, Azam A, Segal S, *et al*. Chronic postsurgical pain and persistent opioid use following surgery: the need for a transitional pain service. *Pain Manag* 2016;6:435–43.
20 Baker DW. History of the joint Commission's pain standards: lessons for today's prescription opioid epidemic. *JAMA* 2017;317:1117–8.
21 Manchikanti L, Fellows B, Ailinani H, *et al*. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician* 2010;13:401–35.
22 Clarke H, Soneji N, Ko DT, *et al*. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ* 2014;348:g1251.
23 Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;323:224–8.
24 Riley RD, Hayden JA, Steyerberg EW, *et al*. Prognosis research strategy (progress) 2: prognostic factor research. *PLoS Med* 2013;10:e1001380.
25 Hemingway H, Croft P, Perel P, *et al*. Prognosis research strategy (progress) 1: a framework for researching clinical outcomes. *BMJ* 2013;346:e5595.
26 Riley RD, Moons KGM, Snell KIE, *et al*. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019;364:k4597.
27 Guimarães-Pereira L, Reis P, Abelha F, *et al*. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. *Pain* 2017;158:1869–85.
28 Humble SR, Dalton AJ, Li L. A systematic review of therapeutic interventions to reduce acute and chronic post-surgical pain after amputation, thoracotomy or mastectomy. *Eur J Pain* 2015;19:451–65.
29 Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. *Eur J Cardiothorac Surg* 2009;36:170–80.
30 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
31 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.

32 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
33 Debray TPA, Damen JAAG, Snell KIE, *et al*. A guide to systematic review and meta-analysis of prediction model performance. *BMJ* 2017;356:i6460.
34 Moons KGM, de Groot JAH, Bouwmeester W, *et al*. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the charms checklist. *PLoS Med* 2014;11:e1001744.
35 Bramer WM, de Jonge GB, Rethlefsen ML, *et al*. A systematic approach to searching: an efficient and complete method to develop literature searches. *J Med Libr Assoc* 2018;106:531–41.
36 Geersing G-J, Bouwmeester W, Zuithoff P, *et al*. Search filters for finding prognostic and diagnostic prediction studies in MEDLINE to enhance systematic reviews. *PLoS One* 2012;7:e32844.
37 Jackson JL, Kuriyama A, Anton A, *et al*. The accuracy of Google translate for Abstracting data from Non-English-Language trials for systematic reviews. *Ann Intern Med* 2019;171:677–9.
38 Bramer WM, Milic J, Mast F. Reviewing retrieved references for inclusion in systematic reviews using endnote. *J Med Libr Assoc* 2017;105:84–7.
39 Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–37.
40 Jackson D, Turner R. Power analysis for random-effects meta-analysis. *Res Synth Methods* 2017;8:290–302.
41 Trivella M, Altman DG. *Systematic reviews of prognostic factor studies: thesis (D Phil)*. 2005. University of Oxford, 2005.
42 Tierney JF, Stewart LA, Ghersi D, *et al*. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
43 Altman DG, McShane LM, Sauerbrei W, *et al*. Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration. *BMC Med* 2012;10:51.
44 Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815–34.
45 DerSimonian R, Laird N. Meta-Analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
46 Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
47 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
48 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101–5.
49 Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3443–57.
50 Foroutan F, Guyatt G, Zuk V, *et al*. Grade guidelines 28: use of grade for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol* 2020;121:62–70.