BMJ Open

Efficacy of esketamine for chronic post-thoracotomy pain: protocol for a systematic review and meta-analysis

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To cite: Juan S, Lu X, Zhou J, *et al*. Efficacy of esketamine for chronic post-thoracotomy pain: protocol for a systematic review and meta-analysis. *BMJ Open* 2024;**14**:e092131. doi:10.1136/bmjopen-2024-092131

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-092131).

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Received 07 August 2024
Accepted 05 December 2024

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ABSTRACT

Introduction Chronic post-thoracotomy pain (CPTP) is a persistent and disabling condition affecting a significant proportion of patients after thoracotomy and posing a challenge for clinicians, despite advances in surgical and pain management strategies. Esketamine, the S-enantiomer of ketamine, has emerged as a promising therapeutic agent for various pain conditions, with evidence for its effectiveness in alleviating acute and chronic pain. This systematic review and meta-analysis will be conducted to assess the efficacy of esketamine in treating CPTP, and evaluate its effectiveness in reducing pain intensity, improving functional outcomes, and reducing opioid consumption, as well as its adverse effects.

Methods and analysis Computer-based literature retrieval in the PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang database and China Science and Technology Journal Database (VIP) for randomised controlled trials will be conducted from database inception to April 2024, with no restrictions on the language of publication. Eligible trials will be those focused on esketamine use to prevent and treat CPTP in adult patients; trial groups will have received esketamine and control groups will have been treated with placebo, standard treatment or other non-esketamine medications. Primary outcome measures can include the incidence of CPTP at 3 months, 6 months or 12 months postoperatively. Secondary outcome measures will encompass Visual Analogue Scale and Numerical Rating Scale Scores for rest and movement at different postoperative timepoints, the total number and effective number of patient-controlled analgesia button presses, total consumption of sufentanil, rate of rescue analgesia, and the occurrence of postoperative adverse reactions. Two researchers will independently screen the literature, evaluate its quality and extract the data. Meta-analysis will be performed on literature meeting the quality criteria using Review Manager V.5.3 software.

Ethics and dissemination This review does not require ethical approval. On completion, the results of the review will be submitted to a peer-reviewed journal for publication and/or presented at an academic conference.

Trial registration number PROSPERO, CRD42024526945.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study will apply a systematic review and meta-analysis approach, ensuring a rigorous and unbiased assessment of the existing literature.
⇒ An extensive search across multiple databases and grey literature sources will minimise the risk of missing relevant studies, strengthening the validity and comprehensiveness of the findings.
⇒ Use of meta-analysis will provide quantitative result pooling, leading to more precise estimation of the effects of esketamine on chronic post-thoracotomy pain (CPTP).
⇒ Assessment of risk of bias in included studies acknowledges their limitations and will enhance the reliability of the conclusions, with implications for clinical practice and guidance for future research directions.
⇒ The study may face multiple potential limitations, including publication bias, heterogeneity among studies, small sample sizes and limited data, inconsistency in reporting, lack of long-term data and indirectness of evidence, all of which may compromise the robustness, reliability and applicability of the findings regarding the efficacy of esketamine in managing CPTP.

INTRODUCTION

Chronic post-thoracotomy pain (CPTP) is a debilitating condition that affects a significant proportion of patients undergoing thoracotomy procedures, such as lung resection and oesophageal surgery.[1] The prevalence of CPTP varies widely, ranging from 20% to 70%, depending on the definition and assessment methods used.[2] CPTP can significantly impact patients' quality of life, leading to decreased physical function, emotional distress, and increased use of healthcare resources.[3]

Management of CPTP remains challenging, with multimodal analgesic strategies often employed to address this complex condition;[4] however, despite these efforts, many patients continue to experience inadequate pain relief. Therefore, there is a pressing need to identify novel therapeutic options for effective management of CPTP.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising agent for

treatment of chronic pain conditions, with analgesic, anti-inflammatory and anti-depressive effects,[5] which may contribute to its efficacy in CPTP. However, use of racemic ketamine (a mixture of R-enantiomers and S-enantiomers) is limited by its psychotomimetic side effects, such as hallucinations and disorientation.

Esketamine, the S-enantiomer of ketamine, has been developed as a more selective NMDA receptor antagonist, with potentially fewer side effects. Several clinical trials have evaluated the efficacy of esketamine for various chronic pain conditions, including CPTP, with promising results.[6–8] Esketamine is thought to exert its analgesic effects through multiple mechanisms, including modulation of NMDA receptors, inhibition of different types of cation channels and enhancement of endogenous opioid signalling.[9]

Despite the growing interest in esketamine for CPTP treatment, no comprehensive systematic review and meta-analysis summarising the available evidence has been conducted. A systematic review and meta-analysis of randomised controlled trials (RCTs) evaluating the efficacy of esketamine in CPTP can provide a robust assessment of its therapeutic potential and inform clinical decision-making.

Hence, we present a protocol for a systematic review and meta-analysis of RCTs. The aim of the review is to assess the efficacy of esketamine in the management of CPTP. The primary objective of the review is to evaluate the effectiveness of esketamine in reducing pain intensity compared with placebo or active control agents. Secondary objectives include assessment of the impact of esketamine on opioid consumption, quality of life and adverse events.

METHODS AND ANALYSIS

This systematic review and meta-analysis is registered on the International prospective register of systematic reviews (PROSPERO) platform of the National Institute for Health and Care Research (NIHR; registration number, CRD42024526945). This study adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement and A Measurement Tool to Assess Systematic Reviews guidelines.[10 11] This systematic review will be a secondary research study conducted on previously published literature, thus meeting the criteria for ethical exemption. Any amendments to information provided at registration or in the protocol will be approved by the NIHR.

Search strategy

The systematic review and meta-analysis commenced on 20 July 2024 and the expected completion date is 31 December 2024. A comprehensive search strategy will be employed across PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, andChina Science and Technology Journal Database (VIP), from database inception to April 2024. The search will not be restricted by language, with translation resources used if necessary, and no restrictions will be imposed on the publication period, to capture all relevant studies. The search strategy will be tailored to the specific syntax and capabilities of each database while maintaining a consistent core set of keywords and concepts, including ‘esketamine’, ‘post-thoracotomy pain’, ‘chronic pain’, ‘analgesia’, ‘pain management’, ‘randomized controlled trial (RCT)’ and ‘clinical trial’. For databases with Medical Subject Headings (MeSH), such as PubMed, MeSH terms will be used in addition to keywords in the title and abstract. For databases with specific search filters, such as clinical trial filters in Embase or Medline, these filters will be applied to refine the search results. For Chinese databases, the search terms will be translated into Chinese, and appropriate Chinese keywords will be used. Each database will be searched independently by a designated researcher, and the results will be exported and compiled using reference management software for screening and de-duplication. Hand searching of relevant journals and conference proceedings will be conducted if necessary. In addition, the Chinese Clinical Trial Registry and ClinicalTrials.gov will be searched to identify ongoing or recently completed studies. Furthermore, cross-referencing using the references in the retrieved literature, expert comments and publicly available correspondence, will be performed to identify potential literature. The search strategy, as exemplified by the PubMed database, is as follows: (‘esketamine’(MeSH Terms) OR ‘S(+)-ketamine’(Title/Abstract) OR ‘S-(+)-ketamine’(Title/Abstract)) AND (‘thoracotomy’(MeSH Terms) OR ‘thoracotomy’(All Fields)) AND (‘pain, postoperative’(MeSH Terms) OR (‘pain’(All Fields) AND ‘postoperative’(All Fields)) OR ‘postoperative pain’(All Fields) OR ‘chronic pain’(All Fields)) AND (‘analgesia’(MeSH Terms) OR ‘analgesia’(All Fields)) AND (clinical trial(Publication Type) OR randomized controlled trial(Publication Type) OR ‘clinical trial’(All Fields) OR ‘randomized controlled trial’(All Fields)). The search strategy is included in online supplemental file 1.

Inclusion and exclusion criteria

All studies included in this research must be RCTs, with adult participants aged ≥18 years who have undergone thoracic surgery, with no further restrictions on sex, race or other demographic characteristics. Intervention(s) must include esketamine, which can be used alone or in combination with other medications. The control agent(s) can be a placebo, standard treatment or other non-esketamine medications. Primary outcome measures can include the incidence of CPTP at 3 months, 6 months or 12 months postoperatively. Secondary outcome measures can include: Visual Analogue Scale Score and Numeric Rating Scale Score at rest and during movement at different time points postoperatively; total number and effective number of presses for patient-controlled intravenous analgesia; the total dosage of sufentanil; the rate

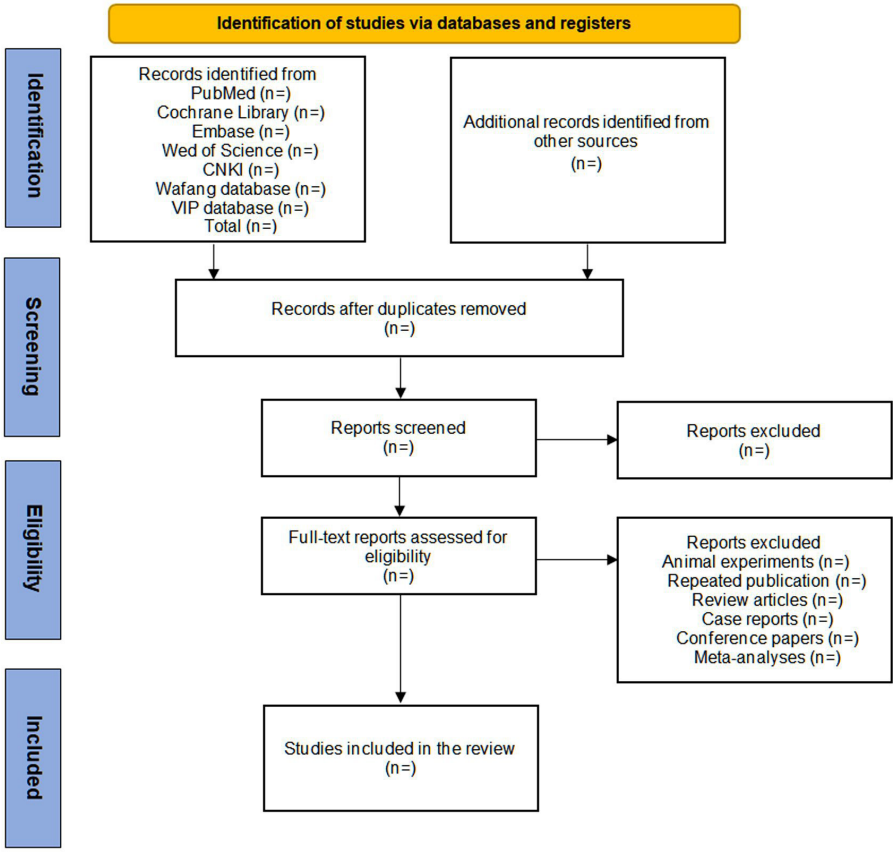

Figure 1 Flow chart illustrating the process of study selection.

of rescue analgesia; and the occurrence of postoperative adverse reactions including nausea and vomiting, respiratory depression, dizziness, salivation and hallucinations, etc.

Non-RCTs, duplicate publications, animal experiments or in vitro studies, research unrelated to the efficacy of esketamine in the treatment of CPTP, studies with incomplete data or with insufficient information in the abstract, and studies deemed to be of low quality based on predefined quality assessment criteria, will be excluded from this study, to ensure the quality and accuracy of the systematic review and meta-analysis.

Study selection

Two independent reviewers will screen the titles and abstracts of identified studies to determine their eligibility, based on the predefined inclusion and exclusion criteria. Endnote V.X9 (Thomson ResearchSoft, Stanford, Connecticut, USA) will be used for deduplication of the literature. The full texts of potentially eligible studies will then be retrieved and assessed for final inclusion. Any discrepancies in eligibility assessment between the two reviewers will be resolved through discussion or, if necessary, consultation with a third reviewer. The flow chart illustrating the process of study selection is presented as figure 1.

Data extraction

A standardised data extraction form will be developed, encompassing study characteristics, patient demographics, intervention details and outcome measures. Two independent researchers will extract data from each study, to prevent bias and identify discrepancies. Extracted variables will include study details (the first author and publication date), patient demographic characteristics (age, sex, body weight or body mass index, and type of surgery), specific details of interventions (administration route and dosage of esketamine and control drugs), and both primary and secondary outcome measures. Extracted data will be entered into a database for analysis, with regular updates for accuracy. Discrepancies will be resolved through discussion, with a third researcher consulted if necessary.

During this review process, we will address incomplete, suppressed, or missing data by first contacting authors to request clarification or data, or trying to calculate from the available information in relevant studies (eg, means and SDs from medians and IQRs). If unavailable, affected studies will be excluded to ensure integrity and reliability. We will disclose this exclusion in our methodology and discuss its implications on the interpretation and generalisability of results, maintaining rigour and transparency in our review process.

Risk of bias assessment

In our study, the risk of bias assessment will be performed for the primary outcome. The risk of bias in the included RCTs will be assessed using the Cochrane Collaboration's tool, considering key domains, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Each domain will be judged as having 'low risk', 'high risk' or 'some concerns' of bias.[12] Two independent researchers will perform the risk of bias assessment for each included RCT, and discrepancies will be resolved through discussion or consultation with a third researcher if necessary. The results will be summarised and presented, providing an overview of potential biases in the studies included in the meta-analysis.

Statistical analysis

Review Manager V.5.3 software will be used to analyse the data from the final included literature that meet the criteria for meta-analysis; for studies that do not meet the criteria, only descriptive analysis will be performed. Assuming consistent measurement methods and tools, mean difference values will be used to assess effect size for selected study indicators, which are all continuous data; otherwise, the standardised mean difference will be adopted. All effect indicators will be presented with 95% CIs, and the significance level for all statistical analyses will be set at $p \leq 0.05$. Generally, heterogeneity will be assessed based on the I^2 statistic and value of p to determine the use of a fixed-effects model ($p > 0.1$ and $I^2 < 50\%$, low heterogeneity among studies) or a random-effects model ($p \leq 0.1$ and $I^2 \geq 50\%$, high heterogeneity among studies). In our opinion, if the heterogeneity is small, there will be no statistically significant difference in the comparison of the final pooled results of the random-effects and fixed-effects models; while only random-effects models can be used when the heterogeneity is significant. Therefore, we will employ the random-effects model in all analyses. Subgroup analysis and sensitivity analysis will be performed to identify sources of heterogeneity. Sensitivity analysis will be conducted where the studies with a high risk of bias are removed, to examine whether a single study has a significant impact on the overall effect size. Subgroup analysis (eg, administrations and doses of ketamine; surgical procedures; pain at different time points after surgery; acute and chronic pain intensity; different patient subgroups; postoperative scores at rest and during movement at different time points; complications; adverse reactions; supplemental analgesics such as opioid consumption, etc) will be conducted if sufficient data are available. Moreover, meta-regression, if possible, will be used to assess the potential impact of certain variables. If at least 10 studies are included, publication bias will be assessed using funnel plots and Egger's test.[13 14] The quality of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach.[15]

Patient and public involvement

None.

ETHICS AND DISSEMINATION

This review does not require ethical approval. On completion, the results of the review will be submitted to a peer-reviewed journal for publication and/or presented at an academic conference.

DISCUSSION

Esketamine is a novel and rapidly acting antidepressant, with gradually recognised unique pharmacological mechanism and potential therapeutic effects in the field of pain management, particularly in the treatment of chronic pain.[16] As the right-handed enantiomer of ketamine, esketamine exhibits strong antagonism effects via NMDA receptors, through which it can inhibit the transmission of pain signals, thereby reducing pain sensation.[17] Furthermore, esketamine exerts analgesic effects through various other mechanisms, including binding to opioid receptors and inhibiting pain hypersensitivity.[18] CPTP is a common complication that significantly impacts patients' recovery and quality of life, and the management of CPTP by conventional analgesic drugs often has shortcomings such as insufficient efficacy and pronounced side effects.[19] Preliminary studies have indicated that esketamine can effectively alleviate pain intensity in patients with CPTP and improve their quality of life.[7 8] The rapid onset of esketamine action facilitates significant analgesic effects for patients within a short period. Additionally, esketamine is reported to reduce the required dosage of opioid drugs, lowering the risk of associated side effects.[20] Despite preliminary research showing its potential value, the precise details of esketamine efficacy and safety for control of CPTP, however, require further confirmation through systematic scientific evaluation.

The aims of the study described in this protocol are to comprehensively evaluate the efficacy and safety of esketamine for the treatment of CPTP, through systematic review and meta-analysis. This research is expected to fill the gap in the current literature regarding esketamine application in this specific field and provide evidence-based treatment options for clinicians. We expected that esketamine can demonstrate significant analgesic effects, which may emerge as a novel strategy for managing CPTP, ultimately improving patients' quality of life and reducing the burden on healthcare.

This systematic review and meta-analysis are expected to provide additional evidence for the existing literature by providing a comprehensive and up-to-date assessment of the efficacy of esketamine in CPTP management. The findings may have important implications for clinical practice, guiding healthcare professionals in selecting appropriate analgesic strategies for patients following thoracotomy. Additionally, the results may inform future research by identifying areas where further investigation

is needed. For example, if certain patient subgroups are found to benefit more from esketamine than others, this may warrant further exploration in future studies. Additionally, if certain adverse reactions are identified, further research may be needed to investigate the underlying mechanisms and potential risk factors.

Despite the comprehensive and rigorous design of this study, it has some potential limitations. First, the varying quality of the included studies may result in heterogeneity of the studies we reviewed, thereby affecting the reliability of the final results. Second, differences in patient characteristics, surgical methods, pain assessment tools, and the dosage and duration of esketamine use among different studies may increase data heterogeneity and make interpretation more challenging. Lastly, due to potential publication bias (such as unpublished negative results), our analysis may not fully reflect the true effects of esketamine. In addition, our study does share some similarity with existing studies to a certain extent. For instance, Clephas *et al* conducted a systematic review with meta-analysis to identify and summarise the evidence of all prognostic factors for chronic postsurgical pain after lung and pleural surgery.[21 22] More recently, Zhaksylyk *et al*[23] performed a systematic review with meta-analysis of RCTs to validate the impact of ketamine on pain-related outcomes after thoracotomy. Ketamine can lower acute pain levels and morphine use after thoracotomy, yet with no data to assess the long-term effect of ketamine on chronic pain. Similarly, Moyse *et al*[24] also intended to identify the efficacy of ketamine in post-thoracotomy pain management, but with insufficient evidence for supporting ketamine as a preventative agent for chronic pain. However, and importantly, the novel contribution of our study will be that we will pay special attention to specific surgery (ie, thoracotomy) and specific drug (ie, esketamine), and dig into both the chronic and acute post-thoracotomy pain based on expanded literature numbers, which will be more targeted to guide clinical pain management.

In conclusion, the proposed systematic review and meta-analysis on the efficacy of esketamine for CPTP has the potential to significantly contribute to the field of pain management. By providing a comprehensive and robust assessment of the effectiveness and safety of esketamine, this study may help guide clinical practice and inform future research, ultimately leading to improved pain management strategies for patients undergoing thoracotomy.

Contributors Conceptualisation: SJ and XL. Methodology: XL, JZ and GW. Validation: XL, GW and YY. Writing the original draft: SJ and YY. Writing the review and editing: SJ, XL and YY. All authors have reviewed and given their approval to the final version of this manuscript. JZ is responsible for the overall content as guarantor.

Funding This study was supported by the Joint Fund for Science and Technology Research and Development Program of Henan Province [Applied Research and Development Category, Project ref 232103810054]. The sponsor and funder had no involvement in the study design, data collection, management, analysis, or interpretation, nor did they contribute to the writing of the research or the decision to submit it for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Gupta R, Van de Ven T, Pyati S. Post-Thoracotomy Pain: Current Strategies for Prevention and Treatment. *Drugs (Abingdon Engl)* 2020;80:1677–84.
2 Rodriguez-Aldrete D, Candiotti KA, Janakiraman R, *et al*. Trends and New Evidence in the Management of Acute and Chronic Post-Thoracotomy Pain-An Overview of the Literature from 2005 to 2015. *J Cardiothorac Vasc Anesth* 2016;30:762–72.
3 Marshall K, McLaughlin K. Pain Management in Thoracic Surgery. *Thorac Surg Clin* 2020;30:339–46.
4 Miyazaki T, Doi R, Matsumoto K. Post-thoracotomy pain syndrome in the era of minimally invasive thoracic surgery. *J Thorac Dis* 2024;16:3422–30.
5 Hirota K, Lambert DG. Ketamine; history and role in anesthetic pharmacology. *Neuropharmacology* 2022;216:S0028-3908(22)00230-1.
6 Wang M, Xiong H-P, Sheng K, *et al*. Perioperative Administration of Pregabalin and Esketamine to Prevent Chronic Pain After Breast Cancer Surgery: A Randomized Controlled Trial. *Drug Des Devel Ther* 2023;17:1699–706.
7 Lei Y, Liu H, Xia F, *et al*. Effects of Esketamine on Acute and Chronic Pain After Thoracoscopy Pulmonary Surgery Under General Anesthesia: A Multicenter-Prospective, Randomized, Double-Blind, and Controlled Trial. *Front Med* 2021;8:693594.
8 Yan H, Chen W, Chen Y, *et al*. Opioid-Free Versus Opioid-Based Anesthesia on Postoperative Pain After Thoracoscopic Surgery: The Use of Intravenous and Epidural Esketamine. *Anesth Analg* 2023;137:399–408.
9 Zhang X, Zhang N, Liu D, *et al*. Research advances in the clinical application of esketamine. *Ibrain* 2022;8:55–67.
10 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
11 Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
12 Higgins JPT, Thomas J, Chandler J, *et al*. *Cochrane handbook for systematic reviews of interventions, 2nd edn*. Chichester: John Wiley & Sons, 2019.
13 Peters JL, Sutton AJ, Jones DR, *et al*. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991–6.
14 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.

15 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
16 Fernandes M, Schelotto M, Doldi PM, *et al*. IMPORTANCE trial: a provisional study-design of a single-center, phase II, double-blinded, placebo-controlled, randomized, 4-week study to compare the efficacy and safety of intranasal esketamine in chronic opioid refractory pain. *F1000Res* 2021;10:42.
17 Mion G, Himmelseher S. Esketamine: Less Drowsiness, More Analgesia. *Anesth Analg* 2024;139:78–91.
18 Duan C, Zhu Y, Zhang Z, *et al*. Esketamine inhibits the c-Jun N-terminal kinase pathway in the spinal dorsal horn to relieve bone cancer pain in rats. *Mol Pain* 2024;20:17448069241239231.
19 Arends S, Böhmer AB, Poels M, *et al*. Post-thoracotomy pain syndrome: seldom severe, often neuropathic, treated unspecific, and insufficient. *Pain Rep* 2020;5:e810.
20 Liu J, Yin J, Yin J, *et al*. Effect of esketamine-based opioid-sparing anesthesia strategy on postoperative pain and recovery quality in patients undergoing total laparoscopic hysterectomy: A randomized controlled trail. *Heliyon* 2024;10:e24941.
21 Clephas PRD, Hoeks SE, Trivella M, *et al*. Prognostic factors for chronic post-surgical pain after lung or pleural surgery: a protocol for a systematic review and meta-analysis. *BMJ Open* 2021;11:e051554.
22 Clephas PRD, Hoeks SE, Singh PM, *et al*. Prognostic factors for chronic post-surgical pain after lung and pleural surgery: a systematic review with meta-analysis, meta-regression and trial sequential analysis. *Anaesthesia* 2023;78:1005–19.
23 Zhaksylyk A, Abdildin YG, Sultangazin S, *et al*. The impact of ketamine on pain-related outcomes after thoracotomy: a systematic review with meta-analysis of randomized controlled trials. *Front Med (Lausanne)* 2024;11:1394219.
24 Moyse DW, Kaye AD, Diaz JH, *et al*. Perioperative Ketamine Administration for Thoracotomy Pain. *Pain Physician* 2017;20:173–84.