Cerebrospinal fluid biomarkers of neuroinflammation and postoperative neurocognitive disorders in patients undergoing orthopaedic surgery: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Postoperative neurocognitive disorders (PNDs) are characterised by gradual cognitive decline or change occurring after anaesthesia and surgery, and they are common in patients undergoing orthopaedic surgery. The onset of PNDs has been associated with dementia or other types of neurocognitive disorders in later life. Moreover, cerebrospinal fluid (CSF) biomarkers of neuroinflammation, including amyloid beta-40 peptide, amyloid beta-42 peptide, total tau protein, phosphorylated tau protein and neurofilament light chain, have been reported to be crucial in several high-quality clinical studies on PNDs. However, the role of these biomarkers in the onset of PNDs remains controversial. Therefore, this study aims to determine the association between CSF biomarkers of neuroinflammation and the onset of PNDs in patients undergoing orthopaedic surgery, which will provide novel insights for investigating PNDs and other types of dementia.

Methods and analysis This systematic review and meta-analysis will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. Moreover, we will search MEDLINE (via OVID), EMBASE and the Cochrane Library without any language and date restrictions. Observational studies will be included. Two reviewers will independently perform the entire procedure, and disagreements will be settled by discussion between them and consultation with a third reviewer. Standardised electronic forms will be generated to extract data. The risk of bias in the individual studies will be evaluated using the Newcastle-Ottawa scale. All statistical analyses will be performed using the RevMan software or the Stata software.

Ethics and dissemination This study will include peer-reviewed published articles; thus, no ethical issues will be involved. Further, the final manuscript will be published in a peer-reviewed journal.

PROSPERO registration number CRD42022380180.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This study will be performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.
⇒ Retrieveable grey literature will be recorded in the screening process to provide a reference for reasonable evaluation of the publication bias of the study.
⇒ The limitation of the study is that we primarily focus on the articles published in English due to the restriction of databases.
⇒ The study will only focus on orthopaedic surgery and neuroinflammation biomarkers in cerebrospinal fluid.

INTRODUCTION
Postoperative neurocognitive disorders (PNDs) are characterised by gradual cognitive decline or change occurring within 1 year after anaesthesia and surgery. Elderly patients comprise a major proportion of the population with PNDs. In the relevant literatures, PNDs can significantly prolong hospitalisation and increase mortality in the future. Besides, previous studies have reported that patients with PNDs have higher risk of developing dementia or long-term cognitive disorders. Although recent studies have demonstrated a significant role of neuroinflammation in the onset and development of PNDs, traditional anti-inflammatory treatments were found to exhibit contradictory effects on PNDs. Further, treatments found to be effective in preclinical experiments may fail to exhibit similar effects in clinical practice or may lack evidence for the use in human beings. A recent study reported that precautionary measures and
management of perioperative risk factors are still the best methods to decline the incidence of PNDs, indicating the importance of early identification of risk factors for PNDs.

Although many high-quality studies have investigated the association between neuroinflammation and PNDs, and have reported the risk factors and the effective prediction models for the onset of PNDs to the best of our knowledge, no accurate biomarker-based prediction models have been widely accepted and used in the routine clinical practice. This may be attributed to many factors such as different sample sizes, multiple mixed factors, only single predictive biomarker, and impractical biomarkers. Therefore, determining practical factors useful for the early identification of PNDs is of great importance in anaesthesia management and drug target designing. Owing to the presence of the blood-brain barrier and blood-cerebrospinal fluid (CSF) barrier, CSF biomarkers can better detect minor changes in the central nervous system than systemic body fluid biomarkers. In addition, systemic inflammatory cytokines cannot completely represent neuroinflammation in the ageing brain and are influenced by various factors, such as surgical trauma. Furthermore, both neuroinflammation and cognitive dysfunction are important features of PNDs and neurodegenerative diseases, and some types of PNDs (eg, postoperative delirium (POD) and postoperative cognitive disorder (POCD)) have been reported to be closely associated with long term cognitive decline or share similar pathways with other neurocognitive disorders. Therefore, it is reasonable to consider the effectiveness of CSF biomarkers of neuroinflammation for the early identification of PNDs.

Accumulation of amyloid beta (Aβ), whose primary forms are amyloid beta-40 peptide and amyloid beta-42 peptide (Aβ40 and Aβ42), in the brain is considered an early event in the pathogenesis of Alzheimer’s disease (AD). Tau protein is one of the many microtubule-associated proteins in neurons that have an important function of regulating microtubules to ensure proper cytoskeletal organisation and trafficking. Its ability to adopt various structural states is essential for its function and pathological properties. Meanwhile, abnormally phosphorylated tau protein (p-tau) can promote the assembly of other microtubule-associated proteins, further worsening microtubule destabilisation. The cerebral levels of both p-tau and total tau (t-tau) in combination with Aβ are meaningful biomarkers for the prediction and diagnosis of AD. The neurofilament light chain (NFL) is a neuron-specific component of the axonal cytoskeleton that can enter the extracellular space after axonal injury or death. NFL has been confirmed to be a useful prognostic biomarker for predicting cognitive decline in patients with Parkinson’s disease and AD. Hence, this study aims to determine the association between the CSF biomarkers of neuroinflammation and the risk of developing PNDs.

The Nomenclature Consensus Working Group has redefined and reclassified perioperative neurocognitive disorder in 2018, in which POD, delayed neurocognitive recovery and POCD are recognised as a part of the continuous spectrum of PNDs. However, in the previous studies published before 2018, delayed neurocognitive recovery was recognised as part of POCD, which will be adopted to ensure all articles about cognitive decline after surgery being fully searched in our study. Many studies have reported that an increasing number of the ageing populations underwent orthopaedic surgery in recent years, and they had a high risk of developing PNDs. Hence, this study aims to determine the association between the CSF biomarkers of neuroinflammation and the risk of developing PNDs in patients undergoing orthopaedic surgery. The aimed biomarkers are Aβ42, Aβ40, t-tau, p-tau, NFL and the ratio of any two of these biomarkers.

METHODS AND ANALYSIS
This systematic review and meta-analysis will be performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement and its protocol will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols checklist. The study, registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42022380180, will be conducted from October 2022 to November 2023. Any changes or amendments made during the review process will be updated in the registration record and reported in the final manuscript.
Eligibility criteria

Only published (including electronic published and printed) or in-press articles from peer-reviewed journal will be included. Studies will be included according to the criteria described below.

Participants

Inclusion criteria

We will include the following studies. First, studies on adult patients who underwent orthopaedic surgery (including hip arthroplasty, knee arthroplasty, fracture surgery and spinal surgery) regardless of the specific anaesthesia methods used. Second, studies in which patients are classified into PNDs and non-PNDs groups and in which CSF biomarkers of neuroinflammation are measured separately for the two groups. Third, studies stating the diagnostic criteria or definition of PNDs. POD is mainly diagnosed using the Confusion Assessment Method (CAM) or the Diagnostic and Statistical Manual of Mental Disorders, Fourth/Fifth Edition (DSM IV/V), and others. POCD is primarily assessed using a battery of neuropsychological tests (NPT) or a single NPT scale, which may include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), and others. Fourth, studies reporting the onset of PNDs within 1 year after surgery. Finally, studies on patients with and without pre-existing neuropsychiatric disorders (eg, dementia) will be included if data of the two subgroups are provided separately.

Exclusion criteria

We will exclude the following studies. First, studies on patients with pre-existing neuropsychiatric diseases that significantly affect cognitive assessment and in which the data of these patients cannot be completely isolated from cognitively normal patients. Second, studies using experimental animals as subjects. Finally, case reports, conference abstracts, study protocols and reviews will be excluded.

Comparators

The comparators were defined as patients who did not develop into PNDs after orthopaedic surgery.

Outcomes

The primary outcome will be the association between the incidence of PNDs and levels of neuroinflammation biomarkers (including \( A_40 \), \( A_42 \), t-tau, p-tau, NFL and the ratio of any two of these biomarkers) in CSF. In addition, according to the diagnosis time of cognitive decline, POCD will be divided into delayed neurocognitive recovery (cognitive impairment occurred within 30 days after surgery) and POCD (cognitive decline occurred from 30 days to 12 months after surgery) in the meta-analyses process. If the included studies report the incidence of PNDs (especially POCD) at various time points in the trial, we will select the same time point as the primary outcome when the studies have similar assessment time points. Otherwise, we will choose the longest time point as the primary outcome.

Study design

Observational studies will be included, such as cohort studies, case–control studies (or nested case–control studies) and cross-sectional studies.

Information sources and search strategy

Under the scientific guidance of an experienced librarian, a comprehensive and systematic retrieval will be conducted in May 2023 using the following three major electronic bibliographic databases: MEDLINE (via OVID), EMBASE and the Cochrane Library. All retrieval strategies will be developed and revised according to the Peer Review of Electronic Search Strategies checklist. Primary search will be conducted to obtain more potential studies using text words (free words) and subject heading index terms (eg, MeSH, Medical Subject Headings in MEDLINE) which will be adjusted or altered to match each database. Part of the retrieval terms and text words are as follows: “cerebrospinal fluid”, “biomarkers”, “neuroinflammation”, “tau proteins”, “amyloid beta-peptides”, “neurofilament proteins”, “postoperative cognitive complications”, “postoperative delirium”, “postoperative cognitive disorders” and “orthopaedic procedures”. A detailed draft retrieval strategy of all databases is displayed in online supplemental material 1. Furthermore, grey literature, including unpublished and ongoing trials, will be identified by searching ClinicalTrials.gov and WHO International Clinical Trials Registry Platform. Subsequently, a manual search will be performed for identifying related articles cited in the included studies/reviews. Google Scholar will be searched as a supplementary database to identify more relevant published references. If required, study authors will be contacted for obtaining the full text and related details. Only studies on human subjects will be retrieved, without any language and date restrictions. An updated retrieval will be conducted before submitting the final manuscript for wider inclusion.

Study records

Data management and selection process

Two reviewers will independently perform the complete database retrieval and screening process. Divergences will be settled first by discussion, and then by consulting a third reviewer. All research results will be imported into the reference management software EndNote (VX9). After removing the duplicates, preliminary screening will be performed, where the titles and abstracts of the studies will be screened to select articles according to the eligibility criteria. Subsequently, the full text of the articles will be downloaded and imported into EndNote for further screening. If necessary, study authors will be contacted for additional data to determine the eligibility of the articles. Finally, we will record the reasons for excluding articles. The screening process will be shown in figure 1.
Data collection process and data items

Using the standardised electronic form that was generated and pretested previously, two reviewers will independently extract the following data: (1) research characteristics, including the first author and publication year, country, study design and sample size; (2) patient demographics, including age, sex, education years, preoperative MMSE scores, type of anaesthesia, diagnostic criteria and assessment time and (3) outcome indicators, including the incidence of PNDs, and the levels of CSF biomarkers of neuroinflammation (Aβ40, Aβ42, t-tau, p-tau, NFL and the ratio of any two of these markers) of both PNDs and non-PNDs groups. The levels of the biomarkers were expressed in the form of mean (SD), median (IQR) or median (range, R), which will be obtained from the included articles. Characteristics of the included studies will be shown in Table 1.

If required, we will contact the study authors to obtain the raw data to ensure data availability for analysis. When multiple eligible articles with overlapping populations or data belong to one study, we will select the article with the largest sample size or the article with complete data on the CSF biomarkers of neuroinflammation. Data presented in figures will be extracted using the GetData Graph Digitizer software (V.2.26, http://www.getdatagraph-digitizer.com/). Similarly, any disagreements will be resolved through discussion and consultation with a third reviewer.

Risk of bias in individual studies

Based on the Newcastle-Ottawa scale (NOS), two reviewers will independently assess the risk of bias of the included articles. NOS is used to evaluate the quality of observational studies based on the following three major components: selection of the study groups, comparability of the study groups and ascertainment of the exposure of interest in cohort study or the outcome of interest in case-control study, with a maximum score of 9. The overall risk of bias of articles will be determined according to the total scores as follows: 0–3, 4–6 and 7–9 indicating low, moderate and high qualities, respectively. Discrepancies will be settled as described earlier.

Data synthesis and statistical analysis

All statistical analyses will be performed using the RevMan software (Review Manager V.5.4, The Cochrane Collaboration, 2020, London, UK) or the Stata software (Stata, V.17.0). According to the inclusion criteria, data synthesis and statistical analysis will be performed in the POD and non-POD groups, as well as in the POCD and non-POCD groups. If the measurement data of the articles are calculated using the same measurement tools and units, the weighted mean difference (WMD) will be used to express the effect size. Otherwise, a standard mean difference (SMD) will be used. We will also calculate WMD (with 95% CI) or SMD (with 95% CI) for continuous outcome variables and OR with 95% CI for dichotomous outcome variables. A p < 0.05 will be considered statistically significant. Data expressed as median with IQR or R will be transformed into mean±SD.

In the case of missing data, we will contact the corresponding author, as described earlier. Descriptive analysis will be performed if the missing data cannot be obtained at

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<th>Table 1</th>
<th>Main characteristics of the studies included in the systematic review and meta-analysis</th>
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<td><strong>Author</strong> (year)</td>
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F%, percentage of the females; MMSE, Mini-Mental State Examination; N-PNDs, non-postoperative neurocognitive disorders; PNDs, postoperative neurocognitive disorders.
all and the number of included records of one biomarker is less than two. Moreover, the I² statistic will be used to evaluate the heterogeneity among the included articles, with a cut-off value of I²≥50% indicating existing or significant heterogeneity. A random effects model will be applied to analyse the data when statistical heterogeneity exists; otherwise, a fixed effects model will be used. In addition, forest plots will be used to visually evaluate heterogeneity. If apparent heterogeneity exists, sensitivity analysis will be conducted to analyse the role of the individual study in statistical heterogeneity. Further, in order to identify the source of heterogeneity, subgroup analyses will be conducted to analyse factors such as type of anaesthesia, diagnosis criteria. If possible, the meta-regression analysis will also be conducted. The impact of potential reporting bias will be evaluated using funnel plots, Egger linear regression test or Begg rank correlation test. The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology. We will discontinue the meta-analysis and only perform a qualitative analysis (a narrative systematic review) when the abovementioned parameters are impossible to deal with obvious heterogeneity.

**Patient and public involvement**

No patient was involved.

**ETHICS AND DISSEMINATION**

The systematic review and meta-analysis will include peer-reviewed published articles and data; thus, no ethical issues will be involved. The final manuscript will be published in a peer-reviewed journal.

**Summary**

This study aims to explore the relationship between the risk of developing PNDs and CSF biomarkers of neuroinflammation, which will help clinicians for early disease identification, precautionary measures making and perioperative management. To the best of our knowledge, this will be the first systematic review and meta-analysis to examine the relationship between CSF neuroinflammation biomarkers (including Aβ42, Aβ40, t-tau, p-tau, NFL and the ratio of any two of these biomarkers) and the risk of developing PNDs in patients undergoing orthopaedic surgery. Furthermore, retrievable gray literature will be recorded in the screening process to provide a reference for reasonable evaluation of the publication bias of the study. The limitation of the study is that we primarily focus on the articles published in English due to the restriction of databases. In addition, this study will only focus on neuroinflammation biomarkers in the CSF of patients undergoing orthopaedic surgery. In the long term, we believe that our study will provide novel insights into detailed mechanisms for investigating PNDs and other types of dementia.

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**Acknowledgements**

The authors thank Beijing Municipal Medical Science Institute for funding this study.

**Contributors**

HF and YL designed and conceived this study, performed study, analysed data and drafted the manuscript of this protocol. XW guided the study retrieval and study analysis process. CW guided data collection and data analysis process. TW guided the study design process and revised the manuscript. HF and YL contributed equally to the manuscript. TW is the corresponding author. All authors read and approved the final manuscript.

**Funding**

This work was supported by Beijing Municipal Medical Science Institute-Public Welfare Development Reform Pilot Project (Capital Medical Research No. 2019-2).

**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.

**Supplemental material**

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