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Perioperative Medicine

STUDY PROTOCOL

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Development of risk prediction model for chronic pain after knee replacement surgery: protocol for an individual patient data meta-analysis

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Abstract

Background Chronic post-surgical pain (CPSP) impacts approximately one in four patients following total knee arthroplasty (TKA) and is associated with reduced function and quality of life. We will conduct a systematic review of prospective studies to identify eligible data and establish an international repository of individual patient data (IPD) on prognostic factors for chronic pain after TKA. This repository will be then used to develop and validate a prediction model for CPSP following TKA.

Methods We will identify eligible studies through a search of MEDLINE, CINAHL, EMBASE, and Cochrane CENTRAL from January 2005 to August 2025. We will include prospective studies that: (1) enrolled adults undergoing elective TKA, (2) assessed perioperative risk factors for CPSP, and (3) measured knee pain longitudinally at least 3 months post-surgery. Pairs of reviewers will independently screen titles and abstracts of retrieved citations and review the full texts of potentially eligible studies. We will reach out to principal investigators or authors of eligible studies to notify them of our initiative and request to receive their IPD into a secured repository, based on a data sharing agreement. We will use a one-stage approach for IPD meta-analysis of factors associated with CPSP following TKA, and development of a risk prediction model.

Discussion We will use anonymized de-identified data for our IPD meta-analysis. This protocol was reviewed and approved by the Hamilton Integrated Research Ethics Board (HiREB). We will develop an online calculator to support our risk assessment model for research and clinical use. This IPD meta-analysis will facilitate the development of a

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robust prognostic model to guide clinical decisions or enrolment in interventional studies, with the ultimate goal of identifying pathways to effective CPSP prevention strategies after TKA.

Trial registration CRD42024591329.

Keywords Chronic post-surgical pain, Knee arthroplasty, Individual patient data meta-analysis, Prediction model, Prognosis

Background

Total knee arthroplasty (TKA) is a cost-effective surgery associated with high rates of symptomatic and functional improvement; however, chronic post-surgical pain (CPSP), dissatisfaction and associated disability develop in approximately 25% of patients (Cheng et al. 2025; Fernández-de-Las-Peñas et al. 2023; Wylde et al. 2018). CPSP is associated with disability and suffering, reduced quality of life, and increased healthcare resource use (Wylde et al. 2018; Cole et al. 2022). It has a multifactorial aetiology, with a wide range of possible biological, psychosocial, and perioperative factors (Wylde et al. 2018; Lewis et al. 2015). Identifying key prognostic factors that increase patients risk for chronic pain is important to personalize patient care and guide the utilization of interventions that may improve patient outcomes (Rosenberger et al. 2023; Yan et al. 2023).

Several studies have explored risk factors for chronic pain after TKA (Wylde et al. 2018; Lewis et al. 2015; Wertli et al. 2014). Our 2022 systematic review and meta-analysis of predictors of CPSP following TKA included 30 studies (26,517 patients) reporting the association for 151 independent prognostic factors, and suggested important associations with greater perioperative pain severity and higher levels of pain catastrophizing (Ashoorion et al. 2022). However, using aggregate data for meta-analysis of prognostic factors has limitations, primarily due to the heterogeneous nature of primary studies (e.g., different definitions and measurement for chronic pain and its predictors, different timepoints to measure pain, different analytical strategies) (Riley et al. 2003; Abo-Zaid et al. 2012). Furthermore, meta-analysis of aggregate data in prognostic studies is restricted to study-level estimates of factor-outcome associations, which may not account for all relevant confounders or risk factors (Buchan et al. 2020). In addition, in an aggregate data meta-analysis, baseline patient characteristics as potential sources of heterogeneity across studies can only be examined at a between-study level, rather than at the individual patient level (Abo-Zaid et al. 2012; Riley et al. 2010). An individual patient data (IPD) meta-analysis is a superior method for synthesizing prognostic factor studies (Trivella et al. 2007; Riley et al. 2009). IPD offers several advantages, including standardization of outcome definitions, the ability to adjust for a consistent set of risk factors across studies, exploration of heterogeneity in predictive performance, reduced risk of overfitting, and the investigation of complex associations (e.g., non-linear prognostic relationships) and covariate interactions (Abo-Zaid et al. 2012; Riley et al. 2010).

Published meta-analysis of aggregate data for prognostic factors for CPSP after TKA have reported inconsistent results (Duan et al. 2018; Harmelink et al. 2017; Wylde et al. 2017; Ghoshal et al. 2023). A recent review of prognostic prediction models for CPSP only found two published models for chronic pain after TKA (Sanchez-Santos et al. 2018; Twiggs et al. 2019) both of which had important limitations (Papadomanolakis-Pakis et al. 2021). They relied on small sample sizes for model development and validation, were limited to a single country and time point, demonstrated poor model performance, and/or omitted several important predictors (e.g., preoperative function, osteoarthritis severity, duration of knee pain, intraoperative factors, procedure-related and postoperative predictors). Using IPD meta-analysis methods offers important advantages over the use of single-dataset approaches to develop risk prediction model, including greater statistical power, enhanced diversity of patient populations and clinical settings that improves external validity and generalizability, and the ability to implement rigorous internal–external cross-validation strategies that assess model transportability across different contexts (Debray et al. 2015; Steyerberg and Harrell 2016).

To date, no risk prediction model specific to chronic pain after TKA has been informed by a IPD meta-analysis, and there is no individual-level registry of patient data from studies on the prevalence of chronic post-surgical pain after TKA (Papadomanolakis-Pakis et al. 2021; Batailler et al. 2022). Thus, we will conduct a systematic review to develop an international repository of individual patient data on perioperative prognostic factors for chronic pain after TKA, followed by an IPD meta-analysis to develop a prediction model.

Methods

Registration and reporting

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist (Moher et al. 2015) in writing this protocol. We have registered our protocol with PROSPERO (CRD42024591329) and will follow PRISMA-IPD guidance to report our findings (Stewart et al. 2015). We

Table 1 A preliminary list of potentially eligible perioperative prognostic factors

Predictor category	Examples
Socio-demographic patient characteristics	age, sex, gender, body-mass Index (BMI), smoking and drinking habits, marital status, living status (living alone, home care, long-term/assisted home, race and ethnicity, education, occupation/employment status, and litigation/insurance
Preoperative psychological and clinical risk factors	preoperative pain catastrophizing, preoperative opioid consumption, preoperative knee pain duration and intensity, chronic pain from previous surgery, preoperative physical and emotional functioning, disease type (rheumatoid arthritis vs osteoarthritis), previous knee arthroscopy, Diabetes, comorbidities affecting mobility, patellar grind and crepitus, knee alignment, state of anterior cruciate ligament (ACL), preoperative Range of Motion, and disease severity (e.g., Kellgren and Lawrence grading), psychological well-being (including anxiety, depression, PTSD, poor coping strategies)
Procedure-related risk factors	operation side, type of procedure, type of implant, duration of procedure, type of anesthesia, opioid use
Post-operative (up to 48 h)	acute post-operative pain, post-operative pain management and medications, mobility, mechanical or surgical complications, duration of hospital stay, infection, duration of postoperative opioid use, postoperative support (e.g., physiotherapy, psychological support, social support)

will follow TRIPOD + AI statement of reporting of the prediction model that use regression or machine learning methods (Collins et al. 2024).

Data sources and eligibility criteria

A medical librarian will perform systematic searches of OVID MEDLINE, CINAHL, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) from January 2005 to August 2025, and search the gray literature using Google Scholar without any language restriction. Our search strategy is provided in Additional File 1. We will screen reference lists of included studies and relevant reviews to find additional eligible studies. We will search the National Institutes of Health Library of Medicine database of clinical trial registries (https://clinicaltrials.gov), the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int), and ISRCTN registry (https://www.isrctn.com) for ongoing or unpublished trials. We will collaborate with our international collaborators and engage senior opinion leaders to identify additional potentially eligible ongoing or published studies.

We will include randomized trials and prospective observational studies (e.g., cohorts, longitudinal or before-after studies, time-series) that: (1) enrolled adults undergoing primary elective unilateral or bilateral TKA, (2) assessed perioperative risk factors for chronic post-surgical pain (including but not limited to any of the factors listed in Table 1), and (3) measured knee pain or reported the incidence of chronic pain at least 3 months after surgery. We will exclude studies of revision or partial knee replacement surgeries and studies with more than 40% missing participants data for pain outcome. This threshold for pain outcome data is selected for pragmatic reason and to avoid biased imputation of primary outcome data (Madley-Dowd et al. 2019).

For the purpose of data collection, we will consider continuous or discrete pain intensity measurement at 3-month post-TKA and any timepoint after that, using a visual analogue scale [VAS] or numerical rating scale [NRS] at any time of day as average pain, pain at rest, or pain with movement. We will prioritize the collection of continuous variables for pain measurements at two or more time points. We will collect and use a binary variable for chronic pain at a certain time point only if a continuous or discrete pain measurement is not available. The 10 cm and 100 mm VAS for pain and the 11-point NRS for pain are established, validated, self-reported measures of pain intensity with proven reliability and good compliance (Karcioglu et al. 2018; Hjermstad et al. 2011). For studies with binary pain data, we will only consider moderate-to-severe pain (≥ 4 cm on a 10 cm VAS or equivalent value on other pain scales) and will consider IASP definition of CPSP (Schug et al. 2019).

Pairs of reviewers will independently screen retrieved records through the searches utilizing standardized, pilot-tested forms within online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; http://systematic-review.net).

Collection and storage of individual patient data

We will contact corresponding authors or principal investigators of eligible studies to inform them of our research study, share a mock table/template spreadsheet with variables of interest, and ask if they are willing to share their de-identified study data. We will invite those who express interest to review our protocol and discuss their data sharing requirements. Subsequently, the data custodian or an institutional representative will be asked to sign a data sharing agreement, outlining the requested data, obligations, data ownership, terms, and authorship arrangement for potential publications. A web link with project details and goals is available for information on our study, including instructions for downloading or uploading encrypted files (www.mac-prosper.ca). To facilitate timely data transfer, we will offer study authors support in preparation and submission of ethics applications and data transfer agreements (if needed). We will request that study authors provide relevant data on candidate predictors and outcomes, even if such data has not been previously reported in their study publication(s).

Data security and governance

Anonymized and de-identified data will be stored in password-protected CSV format for all relevant variables. All file names will include a description of the file contents with the created/modified date and accompanied with metadata files (protocol for this study and our standard operating procedures for data modification and merging, roles and responsibilities regarding data capture, data review and data validation). All cleaned datasets will be stored in password-protected files on a secured server using McMaster University Dataverse (https://borealisdata.ca/dataverse/mcmaster), a secure encrypted server with multifactor authentication that facilitates storage and sharing. The datasets will remain in their original formats, and we will consolidate them into a master dataset for analysis. Only investigators and analysts will have access through password protected computers. Collected data will be stored for a period of five years after open-access publication of our findings – as per our Data Sharing Agreement applications and data transfer agreements. We will follow privacy and confidentiality protections consistent with applicable federal, provincial, and local laws, regulations, and policies.

Risk of bias assessment

The validity and potential bias in studies of prognostic factors will be evaluated using the Quality In Prognosis Studies (QUIPS) tool (Hayden et al. 2013). We will assess the risk of bias across five domains: study participation, study attrition (with ≥ 20% missing data considered high risk of bias), measurement of prognostic factors, outcome measurement, and study confounding. We will use a modified QUIPS tool to rate each domain as either low or high risk of bias, rather than the original response options: low, medium, and high-risk. The individual domain ratings will be used to determine the overall risk of bias for each study. Studies with four or five domains rated as low risk will be considered to have an overall low risk of bias, while studies with two or more domains rated as high risk will be considered to have an overall high risk of bias. Risk of bias assessments will be performed independently and in duplicate. We will assess risk of bias as a potential source of heterogeneity across included studies by conducting subgroup analyses if there is sufficient variability among trials, or through sensitivity analyses by excluding studies at high risk of bias if variability is limited.

Data preparation and synthesis

Data will be inspected for missing values and unusual outliers through range checks for all included variables. We will resolve any issues with the data in collaboration with the original authors. Datasets will be accepted in any format, provided that the data are anonymized, and that variables and categories are clearly labeled in English or an English translation is provided. After satisfactory data control, we will convert each dataset to a common format and rename variables consistently. We will use the original scales of covariate measurements reported, where possible. To ensure compatibility across studies, we will convert variables measuring a common domain (e.g., post-operative acute pain) to the same scale when required. We will combine the individual study datasets into a master dataset, adding a variable to indicate the original study, once the data from each study is cleaned and standardized. Our primary prediction target outcome for developing prediction model will be moderate-to-severe pain (pain score ≥ 4 on a 10 cm VAS) based on average daily pain at 1 year post-TKA. We will additionally conduct sensitivity analyses using alternative definitions (CPSP present at any of 3, 6, or 12 months). Using this approach, individuals with elevated pain at 3 or 6 months whose pain has been resolved by 12 months will be considered non-CPSP in the main model, whereas those who newly develop or maintain moderate-to-severe pain at 12 months will be classified as CPSP cases. We will develop additional separate models using pain at rest and pain with movement as sensitivity analysis.

To maximize clinical utility across different decision points, we will develop two separate prediction models: (1) a preoperative model using only prognostic factors available before surgery, suitable for surgical counseling and shared decision-making, and (2) an extended model incorporating intraoperative and early postoperative variables (e.g., factors listed in Table 1 for postoperative period), suitable for early postoperative risk stratification and targeted intervention within the first days to weeks after surgery.

The methodology of IPD meta-analysis in prognostic research is relatively new compared to that of randomized trials (Abo-Zaid et al. 2012; Debray et al. 2019). Two important methodological considerations in the analysis are: (1) method of meta-analysis (one-stage or two-stage) and (2) handling of missing data, when data are missing for some but not all patients in a single study (within-study missingness) or when data are missing for a prognostic factor for all patients in a given study (between-study missingness). We will use a one-stage method, fitting a single model to all studies in a hierarchical approach. This will involve adding a term to indicate which patient belongs to which study, thereby accounting for the clustering of patients within studies. Our a priori analysis will be based on a multilevel mixed-effects logistic regression that will account for the clustering of patients within studies by including random study-specific intercepts to conduct the one-stage IPD meta-analysis (Burke et al. 2017; Thomas et al. 2017; Kontopantelis 2018).

Handling missing data within and between studies will depend on the extent and mechanism of missingness. To explore the missingness mechanism, we will create an indicator variable for each variable with missing data, coded as "1" for subjects with missing data and "0" for subjects with available data. We will then assess the associations between the indicator variable and the remaining variables. When missingness is < 40%, we will perform multiple imputation using chained equations (MICE) (White et al. 2011; Azur et al. 2011). To increase plausibility of the missing at random assumption, all independent variables and the outcome will be included in the imputation model. Subsequently, missing data will be imputed *m* times, resulting in *m* complete datasets, with *m* being at least equal to the percentage of incomplete cases (White et al. 2011). Each data set will be analysed separately, and results will be combined using Rubin's Rules (White et al. 2011; Burgess et al. 2013). Prognostic factors with > 70% missingness (in combined dataset) and those only available from < 10% of included studies will not be included in the final model. For variables with a missing rate between 40 and 70%, we will use a complete case analysis approach. We will use baseline risk data from the included studies to estimate absolute risk for developing chronic post-surgical pain at different timepoints.

Development and validation of risk prediction model

In developing our model, we will randomly partition the IPD meta-analysis dataset into training (70%) and testing (30%) sets, stratified by study to maintain representativeness (Riley et al. 2019; Joseph 2022). The training set will be used for model development and optimization, while the testing set will be reserved for final performance evaluation. We will systematically evaluate multiple statistical and machine learning techniques to identify the optimal approach for our prediction model. Rather than relying solely on Akaike Information Criterion (AIC) and backward elimination, we will implement regularized regression models including LASSO, Ridge, and Elastic Net regression with cross-validation to determine optimal penalization parameters. These approaches can address multicollinearity and reduce the risk of over fitting the model to the training dataset.

For all continuous prognostic factors, we will first test the linearity assumption. Restricted cubic splines will be used to assess whether the relationship between increasing levels of continuous variables and CPSP is linear or non-linear (i.e., within various ranges of the continuous variable, the measure of association is modified). In addition to testing the linearity assumption, we will check for influential values (i.e., extreme individual data points that could impact the logistic regression model) through visual examination of Cook's distance values. We will also assess multicollinearity between prognostic factors included in the model using the Variance Inflation Factor (VIF) (Royston et al. 2009, 2004). If problematic collinearity is identified (VIF > 5), we will remove collinear variables selecting the one to remain in the model based on clinical relevance upon discussion with our expert panel. We will employ k-fold cross-validation (k = 10) within the training dataset to optimize hyperparameters for each modeling approach. We will leverage model-specific importance metrics (e.g., SHAP values, permutation importance) to identify key predictors across different modeling approaches, providing insight into which prognostic factors consistently demonstrate predictive value.

To communicate the optimistic model performance observed in the derivation cohort, we will summarize discrimination (how well patients with poor outcomes – those with CPSP, are separated from those with better outcomes) and calibration (agreement between probabilities from the prediction model and observed outcome proportions, i.e., the accuracy of the model's predicted probability) (Dankers et al. 2019). The discrimination will be measured by the area under the receiver operating characteristic (ROC) curve (AUC) with a larger AUC indicating a better prediction model and calibration curves will be used to examine calibration graphically (Su et al. 2018; Binuya et al. 2022).

All available TKA datasets will be included in our systematic review and will inform the development of our prediction model. Our primary validation strategy will involve evaluating the final models on the held-out test set to assess generalizability. We will calculate 95% confidence intervals for all performance metrics using bootstrap techniques. Beyond data splitting and cross-validation, we will implement multiple strategies to prevent overfitting, including regularization techniques in all regression-based approaches, pruning parameters in tree-based models, early stopping in boosting algorithms, and dropout in neural network models if employed.

As a supplementary analysis, we will also perform the internal–external cross-validation approach, where IPD from all included studies (say *k* studies) but one is used to develop a risk prediction model, and the IPD from the remaining study will be then used for external validation; this will be repeated a further *k*–1 times by omitting a different study each time. This will provide insight into model performance across different study populations and settings (Royston et al. 2004; Debray et al. 2013). Across all of these, we will pool the observed AUC-ROCs as a macro-AUC-ROC. To validate the calibration of our model, the same procedure will be followed. In each left-out study, we will generate a calibration curve and estimate calibration slopes to check for accuracy of predicted probability and assess for overfitting of the model. We

will combine the calibration slopes to estimate a macro-calibration slope across all studies.

While we will systematically evaluate multiple modeling approaches and advanced machine learning techniques, the selection of our final clinically deployable model will prioritize interpretability, implementability, and consistent performance across diverse settings, even if more complex approaches achieve marginally higher predictive metrics in development datasets. In selection of the final deployable model, we will consider predictive performance (discrimination, calibration, and, where appropriate, decision-curve/net benefit metrics), parsimony and use of routinely available predictors, consistency and stability of performance across internal–external cross-validation settings, and ease of implementation (e.g., ability to embed in a simple risk score or web-based calculator).

A model will be considered acceptable for clinical deployment if it achieves an AUC ≥ 0.70 with good calibration (calibration slope 0.80–1.2) across internal–external validation studies, uses ≤ 15 routinely available predictors, and can be implemented in a format accessible to perioperative clinicians without requiring statistical software or advanced computational resources. If multiple models meet these thresholds, we will select the most parsimonious and interpretable option. More complex models that outperform simpler alternatives only marginally (AUC difference < 0.05) will be reported as exploratory models but will not be recommended as the primary clinical tool.

We will develop user-friendly visual summaries of model predictions and feature contributions to enhance interpretability for clinicians. For implementation purposes, we will consider simplified versions of complex models (e.g., nomograms, risk scores) if they maintain adequate performance compared to the full models.

Discussion

The prognostic factors identified from our IPD meta-analysis will contribute to the development of an advanced prediction model for assessing the risk of CPSP following knee replacement surgery. This will ultimately be used to guide clinical decisions about the most efficient way to prevent CPSP following TKA. Our study focuses exclusively on TKA and does not include unicompartmental knee arthroplasty (UKA), as the risk factors and prognostic pathways for CPSP differ meaningfully between these procedures, though this limits generalizability to the growing UKA population. The results of our study will be published in an open-access scientific journal, and the findings will be presented at relevant national and international conferences. We will share plain language summaries on patient education websites and social media platforms. We will provide access to our risk assessment model for research and clinical use via an online calculator.

Abbreviations

TKA	Total knee arthroplasty
CPSP	Chronic post-surgical pain
IPD	Individual patient data
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
NRS	Numerical rating scale
VAS	Visual analogue scale
QUIPS	Quality In Prognosis Studies
CSV	Comma-Separated Values
MICE	Multiple imputation using chained equations
AIC	Akaike Information Criterion
VIF	Variance inflation factor
ROC	Receiver operating characteristic
AUC	Area under the curve
SHAP	Shapley additive explanations

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13741-026-00672-7.

Additional file1.

Authors' contributions

All authors contributed equally to the development of this protocol. Each author participated in the study design and drafting and revising the protocol. All authors have read and approved the final version of the protocol.

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Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This protocol was reviewed and approved by the Hamilton Integrated Research Ethics Board (HiREB).

Consent for publication

Not applicable.

Competing interests

B. Sadeghirad reports receiving research funding from Canadian Institute of Health Research (CIHR), Michael G. De Groote Institute for Pain Research and Care, and Chronic Pain Centre of Excellence for Canadian Veterans to study different aspects of postsurgical pain. I. Gilron has received funding support from the Canadian Institutes of Health Research SPOR Chronic Pain Network; consultancy fees from Vertex, Reckitt Benckiser, Combigene, and Eli Lilly. J.W. Busse is funded, in part, by a Canadian Institutes of Health Research Canada Research Chair in Prevention & Management of Chronic Pain. A. Iorio reports reports that the Health Information Research Unit and McMaster University are receiving funds from research grants or research service agreements from CIHR, PHAC, CAD, ACP, EBSCO, Bayer, CLS, Novo Nordisk, Roche, Sanofi, Takeda. C. Righolt is employed by the Orthopaedic Innovation Centre and has received institutional research funding from Pfizer for an unrelated study. C. Righolt and E. Bohm have received institutional research funding from DePuy-

Synthes, Zimmer-Biomet, Smith and Nephew, Stryker, and Hip Innovation Technology for unrelated studies. E. Bohm has received consulting fees from Stryker. J. khan reports receiving grant funding from the Canadian Institute of Health Research, Rising Tide Foundation for Clinical Cancer Research, Arthritis Society, Canadian Anesthesia Research Foundation and is personally supported by a Merit Award from the Department of Anesthesiology and Pain Medicine at the University of Toronto. The remaining authors declare that they have no relevant competing interests.

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