Development of Risk Prediction Model for Chronic Pain After Knee Replacement Surgery: Protocol for an Individual Patient Data Meta-analysis

On behalf of McMaster-PROSPER Investigators

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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 chronic pain 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 in duplicate. 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 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.

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.[1-3] CPSP is associated with disability and suffering, reduced quality of life, and increased healthcare resource use.[4] It has a multifactorial aetiology, with a wide range of possible biological, psychosocial, and perioperative factors.[3,5,6] 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.[7]

Several studies have explored risk factors for chronic pain after TKA.[3,6,8] 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.[9,10] 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).[11,12] 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.[13] 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.[12,14] An individual patient data (IPD) meta-analysis is a superior method for synthesizing prognostic factor studies.[15,16] 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.[12,14]

Published meta-analysis of aggregate data for prognostic factors for CPSP after TKA have reported inconsistent results.[17-20] A recent review of prognostic prediction models for CPSP only found two published models for chronic pain after TKA,[21,22] both of which had important limitations.[23] 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). 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.[23,24] 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 [25] in writing this protocol. We have registered our protocol with PROSPERO (CRD42024591329) and will follow PRISMA-IPD guidance to report our findings.[26] We will follow TRIPOD+AI statement of reporting of the prediction model that use regression or machine learning methods.[27]

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 or predictors listed in Table 1.

Our outcome of interest for development of a prediction model will be moderate-to-severe CPSP (pain score ≥ 4 on a 10cm VAS). 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 10cm and 100mm visual analogue scale (VAS) for pain and the 11-point numerical rating scale (NRS) for pain are established, validated, self-reported measures of pain intensity with proven reliability and good compliance.[28,29] For studies with binary pain data, we will only consider moderate-to-severe pain (≥ 4cm on a 10cm VAS or equivalent value on other pain scales) and will consider IASP definition of CPSP.[30]

Pairs of reviewers will independently, and in duplicate 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 store all cleaned datasets in password-protected files on a secure server at McMaster University, accessible only to core members of the IPD meta-analysis group. The datasets will remain in their original formats, and we will consolidate them into a master dataset for analysis. 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. 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.[31] 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 target outcome for developing prediction model will be moderate-to-severe pain (pain score ≥ 4 on a 10cm VAS) based on average daily pain at 3-months, 6-months, and 1year post-TKA. We will develop additional separate models using pain at rest and pain with movement as sensitivity analysis.

The methodology of IPD meta-analysis in prognostic research is relatively new compared to that of randomized trials.[12,32] 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 to conduct the one-stage IPD meta-analysis.[33-35]

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).[36,37] 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.[36] Each data set will be analysed separately, and results will be combined using Rubin's Rules.[36,38] 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.[39,40] 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).[41,42] 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).[43] 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.[44,45]

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.[42,46] 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.

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 chronic pain following knee replacement surgery. This will ultimately be used to guide clinical decisions about the most efficient way to prevent chronic pain following total knee arthroplasty. 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.

List of 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

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.

Availability of data and materials

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

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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Declaration competing interests

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The remaining authors declare that they have no relevant competing interests

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	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)

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