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Predicting poor postoperative pain control after elective spine surgery

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Predicting poor postoperative pain control after elective spine surgery

by

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ABSTRACT

Background

Inadequate postoperative pain control after spine surgery is common and can lead to patient dissatisfaction and poor outcomes. Predictors for poorly controlled pain after spine surgery are unknown and preoperative prognostic tools are not available to aid in the identification of high-risk patients to help facilitate the development of personalized treatments. In this thesis, we performed (1) a systematic review on the predictors associated with poor pain control in surgical patients; (2) performed a retrospective cohort study evaluating predictors of poor postoperative pain control following spine surgery; and (3) developed and validated a clinical prediction score to identify patients at high-risk for developing poor pain control.

Methods

(1) A random-effects model was used to meta-analyze the predictors for poor pain control after surgery in the systematic review. (2) Adults from the *Canadian Spine Outcomes and Research Network* registry who underwent elective cervical or thoracolumbar surgery were included. Preoperative predictors for poor pain control (mean numeric rating scale for pain>4 at rest during the first 24 hours after surgery) were identified using a multivariable logistic regression model. (3) The prediction score was developed and internally validated using a 70:30 split-sample method.

Results

(1) Thirty-three studies representing 53,362 patients were included in the systematic review. Nine significant predictors for poor postoperative pain control were identified across surgical

disciplines. (2) The retrospective cohort study included 1,300 patients, of which 56.7% had poor pain control after surgery. The multivariable model identified that younger age, female sex, preoperative daily opioid use, higher preoperative neck/back pain, higher depression scores on patient health questionnaire-9, ≥3 motion segment surgery, and fusion surgery were associated with poor pain control. (3) Patients identified as low-, high-, and extreme-risk by the score had 32.0%, 63.0%, and 85.0% probability of developing poor pain control, respectively.

Conclusion

Seven significant predictors for poorly controlled pain after spine surgery were identified and incorporated into a prediction score. The score can discriminate patients at higher risk for, and accurately predict the probability of, developing poor pain control after surgery.

PREFACE

- Chapter 2 of this thesis has been published as Yang, M. M. H., Hartley, R. L., Leung, A. A., Ronksley, P. E., Jetté, N., Casha, S., & Riva-Cambrin, J. (2019). Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. *BMJ Open*, *9*(4), e025091. doi:10.1136/bmjopen-2018-025091.[153] This article is published under the CC-BY-NC license, as such, permission to include this chapter in this thesis is not required.
- Chapter 3 of this thesis is original, unpublished, independent work by the authors Yang M, Riva-Cambrin J, Cunningham J, Jetté N, Sajobi TS, and Casha S. This chapter is covered by ethics certificate number REB17-2096 from the University of Calgary Conjoint Health Ethics Board for the project "Predicting Poor Postoperative Pain Control After Spine Surgery" on February 15th, 2018. This chapter will be submitted for publication at a future date.

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- MMHY is the primary (first listed) author for all the work included in this thesis. MMHY is the author who has made the most substantial contribution to the manuscripts "Preoperative predictor for poor acute postoperative pain control: a systematic review and meta-analysis" and "A Clinical Prediction Model for Poor Acute Postoperative Pain Control After Elective Spine Surgery: the Calgary Postoperative Pain after Spine Surgery (CAPPS) score."
- MMHY was involved in all facets for both manuscripts including study conception, study design, data collection, data analyses, data interpretation, created figures and tables, wrote the first draft of the manuscripts, critically appraised all manuscript versions, approved the last version of manuscripts, and revised the manuscripts for publication.

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- JRC was involved with study conception, data interpretation, critical appraisal of all manuscripts, approval of the final manuscript, and study supervision.

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- JC was involved with data collection, data interpretation, critical appraisal of one of the manuscripts, and approval of final manuscript.

LIST OF SYMBOLS, ABBREVIATION AND NOMENCLATURE

Abbreviation	**Definition**
ROC	Receiver operating characteristic
CAPPS	Calgary Postoperative Pain After Spine Surgery
IASP	International Association for the Study of Pain
VAS	Visual analogue scale
NRS	Numeric rating scale
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
PRESS	Peer Review of Electronic Search Strategy
VRS	Verbal rating scale
ASA	American Society of Anesthesiology
BPI	Brief Pain Inventory
PACU	Post anesthesia care unit
PCS	Prospective cohort study
RCS	Retrospective cohort study
GS	General surgery
CI	Confidence interval
BMI	Body mass index

TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis
CSORN	Canadian Spine Outcomes and Research Network
FMC	Foothills Medical Center
VIF	Variance inflation factor
SSLR	Stratum specific likelihood ratio
aOR	Adjusted odds ratio
C-statistic	Concordance statistic
ODI	Oswestry disability index
NDI	Neck disability index
PHQ-9	Patient health questionnaire-9
APS-POQ	American Pain Society Patient Outcome Questionnaire

CHAPTER 1: INTRODUCTION

Overview and Goals of Thesis

Currently, there is a lack of understanding of the preoperative patient and surgical procedure related risk factors for poor postoperative pain control following spine surgery.[153] This lack of knowledge precludes clinicians from taking a focused preoperative history on items that may affect postoperative pain and prevents clinicians from providing individualized education on expected pain control following surgery. Further, no prognostic tool is available to clinicians which can be used to inform patients on their chance for developing poor pain control following spine surgery based on their personal risk factors. The inability to identify at-risk patients preoperatively prevents the development of preventative preoperative and perioperative management strategies to improve pain outcomes. As a result, preoperative patient education and implementation of personalized pain management strategies are rarely carried out in the spine surgery population.

The purpose of this thesis is to improve the understanding of the preoperative patient and surgical risk factors for poor postoperative pain control following elective spine surgery and to develop, and internally validate, a clinical prediction score that can identify at-risk patients in the preoperative setting. The addition of this knowledge to the literature will enable clinicians to provide individually tailored preoperative education regarding expected postoperative pain control and to develop personalized clinical-care pathways during the preoperative and perioperative period to improve postoperative pain outcomes.

The three goals of this thesis were (1) to perform a systematic review and meta-analysis of the literature on preoperative predictors of poor acute postoperative pain control after surgery (all disciplines). The significant predictors found in that review were included as candidate variables in a (2) retrospective cohort study evaluating the predictors of poor postoperative pain control following elective spine surgery. Using the significant predictors found in the cohort study, a (3) clinical prediction score was developed and internally validated that would allow clinicians to identify patients at risk for developing poorly controlled postoperative pain in the preoperative setting. Goal (1) will be addressed in Chapter 2 and goals (2) and (3) will be addressed in Chapter 3.

Clinical Background

Definition of Pain

The Taxonomy Committee of the International Association for the Study of Pain (IASP) defines pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[1] Postoperative pain is considered a form of acute pain due to surgical trauma with an inflammatory reaction.[64] It is comprised of several unpleasant sensory, emotional, psychosocial, and mental experiences precipitated by the surgical trauma and associated with autonomic, endocrine-metabolic, physiological, and behavioral responses.[64] Acute postoperative pain may be of nociceptive or neuropathic origin. Pain described as burning, stabbing, or resembling an electric shock suggests a neuropathic origin.[64] Nociceptive pain is usually time-limited and responds well to treatment with opioids. In contrast, neuropathic pain is often chronic and is less responsive to opioid medications.[64]

Measurement of Postoperative Pain

Regular postoperative pain assessments are required to provide optimal postoperative pain care.[32] Frequent pain assessments can inform whether current pain management is adequate and whether changes to the analgesic regimen are required. In difficult to manage cases, the involvement of perioperative pain specialists may be warranted.[32] Since pain is subjective, patient self-report is the primary basis of all pain assessments.[2] Various pain assessment tools have been validated for accuracy in measuring the severity of postoperative pain, and have been validated for intra-patient and inter-rater reliability.[32] Examples of validated pain scores include visual analogue scale (VAS, commonly rated between 0 to 100mm, with 100mm meaning worst pain possible), numeric rating scale (NRS, 11 point scale, between 0 to 10, with 10 meaning the worst pain possible), and Wong-Baker FACES pain rating scale (often used in the pediatric population).[32] When NRS is verbally administered by a research coordinator or a health care professional, it is called the verbal numeric rating scale (vNRS) for pain. The use of one of these validated patient-reported pain scores have become common place to measure the intensity of postoperative pain.[32] However, there is insufficient evidence to recommend one pain assessment tool over the other as it relates to postoperative outcomes.[32]

The subjective experience of pain is multi-dimensional, with biological, psychosocial, and environmental factors influencing the intensity and quality of pain. However, one-dimensional tools such as those described above (e.g., NRS) that are used in the postoperative setting would not capture the complete pain experience. More comprehensive assessments of pain can help determine the type of pain (e.g., visceral, neuropathic, nociceptive), how pain impacts patient

function, and which previous treatment strategies were effective.[56] The short version of the Brief Pain Inventory (BPI) is a 9-item multi-dimensional pain questionnaire that allows patients to rate the severity of their pain at its "worst", "least", "average", and "now" (current pain), and the degree in which their pain interferes with common dimensions of feelings and function.[34] The BPI also measures how pain has interfered with seven different daily activities: general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.[34] While the BPI attempts to quantify the intensity of pain, the McGill Pain Questionnaire attempts to qualify the experience of pain. The McGill Pain Questionnaire is a self-reported pain questionnaire that uses three major classes of word descriptors- 'sensory', 'affective', and 'evaluative' to describe the subjective pain experience of the patient.[106] Patients are presented with a list of 78 words in 20 sections that are related to pain and the patient marks the word that best describes their pain. Although multi-dimensional questionnaires such as the BPI and the McGill Pain Questionnaire are more effective at capturing the subjective experience of pain, these questionnaires were developed and validated for chronic pain patients.[56]

Other multi-dimensional surveys developed for the assessment of acute pain, such as the American Pain Society Patient Outcome Questionnaire (APS-POQ), are not designed to guide clinical care, and are not suitable for frequent reassessments often required in the postoperative period.[57] Although attempts have been made in the perioperative pain literature to use more comprehensive pain assessment tools, unidimensional scales such as the VAS, NRS, and the verbally administered NRS remains the most commonly used tool in the postoperative setting.[56]

In this thesis, the primary outcome was retrospectively collected through patient charts. As such, the institution's standard pain assessment tool was used. The NRS for pain is the standard assessment tool used at the Foothills Medical Center to assess for postoperative pain. Fortunately, NRS is a validated tool for the assessment of postoperative pain and previous studies have demonstrated strong correlation to the VAS and the vNRS for pain.[84] Poor postoperative pain control was defined as patients having a mean NRS>4 at rest in the first 24 hours following surgery. NRS>4 is an accepted threshold for the definition of moderate to severe pain intensity, whereas NRS≤4 has been defined as the threshold for tolerable pain.[54] Additionally, NRS>4 has been previously shown to be associated with increased analgesic (including opioid) requirements in the postoperative period, and increased pain related interferences such as poor sleep, delayed recovery, and decreased patient mobility.[54]

Timing of Postoperative Pain Assessment

There is no consensus regarding the ideal frequency or timing for postoperative pain assessments.[32] In a national survey in France, 94% of their surgical wards performed postoperative pain evaluations at intervals of 4 hours.[50] Frequent assessments for pain may be warranted during the first 48-hours after surgery when the highest proportion of patients have moderate to severe postoperative pain.[32] Conversely, frequency of assessments may be reduced in patients who have adequate pain control without side effects after 24-hours of stable therapy.

Epidemiology and Consequence of Poor Postoperative Pain Control

According to the 2010 Declaration of Montreal, access to pain management is a fundamental human right and is a human rights violation not to appropriately treat pain.[74] While pain is

universal and expected after surgery, there is growing evidence that pain may be inadequately treated in many patients in the acute period after surgery.[59] In the systematic review performed during this thesis (Chapter 2) we found that the incidence of poor pain control ranged between 14.0% to 78.4% across surgical disciplines.[153] To the authors' knowledge, there have not been any discipline-specific studies evaluating the incidence of poor acute postoperative pain control following spine surgery.[153] However, in a sub-group analysis, Sommer et al[137] reported an incidence of poor pain control between 30-64% following spine surgery.

Poor pain control after surgery is a significant factor associated with patient dissatisfaction, delayed recovery, immobility, and prolonged hospital stay.[53] Poor pain control is also associated with adverse effects such as the development of persistent pain after surgery, venous thromboembolic diseases, and, in the elderly, delirium.[53,83,100] Opioids are the first-line agents in the management of moderate to severe acute pain and are often prescribed in the postoperative period.[104] While effective, over-prescription and under-education can lead to improper use of opioids. Overuse can be associated with significant adverse effects such as ileus, respiratory depression, and dependence. Opioid prescription in the perioperative period varies widely and frequently in excess, even following minor surgical procedures.[24] In a study by Brummett et al., the authors showed that the rates of persistent opioid use were 5.9% and 6.5% following minor and major surgery, respectively.[24] Given the current national opioid crisis, judicious and appropriate use of narcotics has been mandated by both Federal and Provincial health bodies in Canada and the USA.[42,55] A personalized preoperative and perioperative pain management strategy based on a patient's risk factors for poorly controlled pain may decrease the reliance on opioids and improve patient outcomes. Studies have identified factors associated with poorer

pain management postoperatively in other surgical disciplines;[153] however, a comprehensive understanding of these factors and their relative importance in spine patients is lacking.

Expectant Care: The Current Management Scheme for Postoperative Pain After Surgery.

The management schemes for acute postoperative pain varies widely between institutions.[96] According to the *Practice Guidelines for Management of Postoperative Pain* published by the American Pain Society, there are three main aspects to optimal postoperative pain management: (1) preoperative education and perioperative pain management planning, (2) multimodal analgesic therapy, and (3) effective transition to outpatient care.[32] Preoperative education and perioperative pain management involve individually tailored education to the patient, including treatment options for management of postoperative pain and expected postoperative pain intensity.[32] This section also recommends that clinicians conduct a proper preoperative assessment of comorbidities that may affect postoperative pain and develop a perioperative pain management plan using a shared decision-making approach. Multimodal analgesic therapy may include local and regional techniques, neuroaxial therapies (e.g., epidural/intrathecal analgesia), cognitive behavioural and psychotherapy, systemic therapy (e.g., acetaminophen, NSAIDs, and opioids), and physical modalities (e.g., transcutaneous electrical nerve stimulation, massage therapy).[32] The last component of postoperative pain management is an effective transition to outpatient care. That includes providing appropriate education to patients on their expected pain course, and a plan to taper analgesic medications after hospital discharge.[32]

The lack of understanding of the preoperative and perioperative risk factors for poor postoperative pain control following elective spine surgery limits clinicians from achieving the

first part of optimal postoperative pain management: "preoperative education and perioperative management planning".[32] This thesis attempts to clarify these risk factors and to develop a simple-to-use clinical prediction score that will aid in the identification of patients at high-risk for inadequately controlled pain following spine surgery.

Methodology & Analysis

Systematic Review & Meta-Analysis

To develop a robust clinical prediction score, care must be taken when selecting candidate variables to be included in the multivariable model. Variables that are included should have potential relevance in predicting the outcome, should add substantial prognostic information beyond what other variables provide, should be discrete and readily interpretable, and should be feasible to collect by the end-user of the prediction score.[51,68,69,135] In this thesis, candidate predictors were scrutinized by a panel of experts using the criteria above and supplemented by a review of the literature of previously known predictors of poor postoperative pain control.

Fourteen different types of literature review have been described, ranging from narrative reviews, systematic reviews, meta-analyses, to scoping reviews.[61] Each type of review has advantages, disadvantages, and different purposes. For example, narrative review is a literature review that describes published materials that provide an examination of recent or current literature.[61] The advantages of a narrative review include the ability to identify and summarize what is previously known about a particular topic. Narrative reviews are useful in identifying gaps in knowledge, and to explore areas of further research. However, a narrative review is often

performed in a non-systematic manner and therefore, subject to bias. Certain studies may be excluded or included in order to support the perspective of the author.[61]

As a result, for this thesis, a systematic review and meta-analysis was selected to facilitate the selection of candidate predictors of poor postoperative pain control after spine surgery. A systematic review seeks to systematically search for, appraise, and synthesize research evidence regarding a specific patient population with a particular disease or condition.[61] Systematic review is often guided by reporting guidelines depending on the types of studies that are included. In this thesis, the meta-analysis of observational studies in epidemiology (MOOSE) guideline was used since the systematic review only included observational studies (e.g., prospective cohort, retrospective cohort, and cross-sectional studies). An essential component of systematic reviews is the inclusion of risk of bias or quality assessment for the included studies. It is crucial to select a risk of bias assessment tool that is designed to capture all potential sources of bias. Depending on the study design (e.g., randomized controlled trial vs. observational studies), different risk of bias tools may be needed to address different sources of bias.[45]

A meta-analysis is a "statistical technique that combines the results of quantitative studies to provide a more precise effect of the results" and often follows a systematic review.[61] The perceived benefit of a meta-analysis is the ability to synthesize all available evidence into a composite measure of association. Multiple small studies that do not show significant associations may together show a significant association after a meta-analysis. For a meta-analysis to be informative, all the included studies should be sufficiently similar to allow pooling of the data.[61] If there is a significant difference in terms of the patient population, outcomes

definition, or interventions used between studies, this makes the statistical interpretation of the meta-analyses more challenging.

There are two main methods to statistically pool results in a meta-analysis: a fixed- or random-effects model.[45] A fixed-effects model assumes there is only "one truth" in the results, and studies only differ due to random error. As a result, studies with larger sample sizes are given weights that are inversely proportional to the result's variance.[45] A random-effects model assumes there is a distribution of truths and studies differ according to random error and between-study variations (e.g., differences in the study population, intervention, and study design).[45] As such, a random-effects model assumes a distribution of the true parameter, and studies with varying sample size are weighed more comparably compared to the fixed-effects model.[45] In this thesis, a random-effects statistical model was used since there are differences between studies, including differences in surgical discipline, timing of postoperative pain assessment, and definition of postoperative pain control.

Due to clinical variations between studies, statistical heterogeneity may arise after a meta-analysis. Statistical heterogeneity exists when the true effect being evaluated differs between studies and may be detectable if the variation between the results of the studies is above that expected by chance.[70] There are two main ways to evaluate for and quantify the degree of heterogeneity; the Cochrane's Q statistics and I^2 statistic.[70] The null hypothesis for the Cochrane's Q statistics is that the treatment effects of all of the studies are equal. The statistical test is based on a chi-square calculation using a k-1 degree of freedom, where k is the number of included studies in the meta-analysis.[70] A significant p-value suggests the null hypothesis can be

rejected, and the alternative hypothesis that at least one study has a different treatment effect may be accepted. The disadvantage of the Cochrane's Q statistics is the lack of power to detect a significant difference in situations when there are few studies and excessive power to detect clinically unimportant heterogeneity when there are many studies.[70] The alternative method of measuring statistical heterogeneity is the I^2 statistics. One of the advantages of the I^2 statistics is that it allows the quantification of the degree of inconsistency between studies. The I^2 statistics represents the proportion of total variability due to between-study heterogeneity.[71] The I^2 statistics has a range between 0 to 100%. By convention, low-, moderate-, and high-degree of statistical heterogeneity refer to an I^2 statistics of <25%, 25-50%, and >50%, respectively.[71] In this thesis, both the Cochrane Q and I^2 statistics were reported since there was a large variation in the number of studies included for each preoperative predictor of poor postoperative pain control. By using both measures, the reader is provided the opportunity to use their judgement on which measure is the most appropriate.

The presence of significant heterogeneity provides an opportunity to explore for covariates that can potentially explain the heterogeneity. The exploration of sources of heterogeneity is often the most exciting aspects of a meta-analysis since it allows for hypothesis generation for future studies that can help explain the variations observed. Heterogeneity can be explored by using stratified meta-analysis and meta-regression.[45] Heterogeneity secondary to publication bias can be explored visually using funnel plots and tested statistically using the Egger and Beggs test.[45] In this thesis, sources of heterogeneity were explored using both stratified meta-analysis, and meta-regression.

Development of a Clinical Prediction Model

As medicine moves towards precision medicine, there is an increasing need for predictive tools to allow clinicians to make decision, based on accurate estimated risk or probability that a specific disease or condition is present or a specific event will occur in the future.[35] Clinical prediction models (also called prediction rules, decision rules, prediction scores) allow clinicians to make evidence-based prediction about future events based on multiple variables or predictors. A famous prediction model is the Framingham Risk Score used to predict the 10-year cardiovascular risk of an individual.[10]

Derivation of Clinical Prediction Models

Prediction model development broadly follows two main steps: model development and validation.[35] Model development aims to develop a prediction model based on relevant and significant predictors using a multivariable model. The model is usually developed from a dataset that contains all possible variables. Variables can include demographic information (e.g., age and sex), patient-reported outcome measures, and any other variables that are considered relevant to the study question. From all the possible variables, a subset of candidate variables is selected for analysis based on a set of clinical and statistical criteria. From these candidate variables, the final model is derived and internally validated.

Internal Validation of Prediction Model

It is crucial for any study developing a new prediction rule to include some form of internal validation to quantify any optimism in the apparent performance of the model.[35] This is

important because quantifying the predictive ability of a prediction model using the same dataset used to derive the model often results in overfitting and optimistic estimates of its performance.[35] Apparent performance can be expressed in terms of discrimination (the ability of the model to distinguish those at high- vs. low-risk of developing the outcome) and calibration (the agreement between predicted and observed probability of the outcome).[142]

There are numerous ways to develop and internally validate a clinical prediction model. Standard techniques include the split-sample design, cross-validation, and bootstrapping.[36] The split-sample design is performed by randomly splitting the dataset into two groups; one for model development and the other for model internal validation. There is no consensus regarding the ideal proportion of patients that should be reserved for model development vs. internal validation.[36] The split-sample technique is ideal for studies of large sample sizes since a portion of the dataset is excluded from the model development cohort. The exclusion of a portion of patients from model development diminishes the statistical power of the multivariable analysis. This could lead to biased regression coefficients, inflated standard errors, and paradoxical association when there are few outcome events relative to the number of covariates assessed.[115] Further, there is no guarantee that the two groups are representative of the target population (e.g., that the predictors are equally distributed between development and validation cohorts), which may limit the generalizability of the model. The benefit of this technique is that the internal validation procedure is applied to an independent sample of patients not used to derive the prediction model and hence reduces the risk of overfitting and inflated optimism of the model's performance.

Cross-validation and bootstrapping are other commonly used techniques to develop and internally validate a prediction model.[36,89] These techniques address the limitation of the split-sample method as they utilize the entire dataset to derive and internally validate the prediction model. In cross-validation, the data is split into a number (k) of equal "folds," or groups.[89] The model is developed on one random group and tested on the remaining groups. This procedure is repeated until each group has been used for derivation of the model k-1 times and for validation one time. The parameter estimates from each iteration can be averaged to produce a model with lower standard errors compared to the split-sampling model.[59] The cross-validation method also avoids the bias associated with the split-sample method since the data is split multiple times across the dataset.

Bootstrapping is a more computationally intensive method that involves taking random samples with replacement from the data and creating sub-groups for model development and validation. This is an iterative process that is repeated hundreds to thousands of times, each time producing a surrogate model for parameter estimation.[89] The advantage of this method is the relatively smaller variance estimation compared to the two methods listed above.

In this thesis, a split-sample design was chosen as the method to develop and internally validate the prediction score due to the relatively large sample size of the database. Further, the reduced chance of over-optimism regarding the model performance was deemed important. We determined *a priori* that we had sufficient power to evaluate 25 degrees of freedom using 70% of the dataset in a multivariable model.

External Validation of Prediction Model

Prediction models are often developed using a discrete set of data from a single institution or collection of institutions. As a result, the generalizability and applicability of these prediction model to a different population needs to be confirmed. As a result, it is strongly recommended to evaluate the predictive performance of the model in a separate population that was not used to derive the initial prediction model.[35] This is called an external validation of the prediction model. Outcome predictions are made for each patient in the external dataset using the original prediction model. The predictive performance is then evaluated by comparing the predicted outcomes to the observed outcomes in the new dataset. Predictive performance can be reported in terms of discrimination and calibration similar to apparent model performance. Common methods to report discrimination include the c-statistic and percentage misclassification ([false positive + false negative]/total x 100%). Calibration can be reported using the Hosmer-Lemeshow Goodness-of-Fit test, calibration plot, or a graphical comparison between the observed vs. predicted probability of the outcome.[7]

Dealing with Missing Data

The appropriate management of missing data is an important component of any well-designed clinical research project. There are numerous ways to deal with missing data, but the goal should be to reduce the risk of bias, maximize the statistical power of the analysis, and obtain appropriate estimates of uncertainty.[60] There are three broad approaches for dealing with missing data: complete case analysis, single imputation, and multiple imputation. The default method of dealing with missing data in many statistical software packages is complete case analysis. In this

method, only variables with complete data are included in the analysis. This is a common technique because it is easy to implement and works with any analysis. Complete case analysis will lead to non-biased results only when the data is 'missing completely at random'. This means the missing values in the data cannot be predicted by the observed and unobserved data.[60] For other types of missing values, this method will lead to biased model estimates and larger standard errors due to smaller sample sizes.[60] Further, depending on the number of missing data in each of the included variables, there can be a significant loss of power with complete case analysis.

Single imputation refers to replacing the missing value with another single value.[60] An example of single imputation is replacing missing values with the mean value of that variable (e.g., replacing all missing values with the mean value for body mass index). For repeated measure studies, the "last observation carried forward" approach is often used. The disadvantage of single imputation is that it does not account for the uncertainty of the missing data. As a result, the standard errors of the estimates are likely to be too small (e.g., overestimating the precision of the results), which can lead to increased chance of committing a type 1 error. Similar to complete case analysis, the effect estimates will be unbiased only if the missing values are 'missing completely at random' and if the aim is to estimate a mean.[60]

In this thesis, multiple imputation was used to deal with missing data. Although the number of missing data points for each variable was small, the different pattern of missing data across 25 candidate variables had a significant impact on the statistical power if complete case analysis had been used. Multiple imputation is a more sophisticated method of addressing missing data. It

aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combines results obtained from each of them (as such the final results will have larger standard errors compared to single imputation).[141] Multiple imputation is also superior to other methods because it can deal with data that are 'missing completely at random' and 'missing at random'. 'Missing at random' means the missing values can be predicted by the observed values in the dataset.[60] As such, there is reduced risk of obtaining biased effect estimates using multiple imputation.

Using this approach, multiple copies of the dataset, with the missing values replaced by imputed values (this fill-in process is repeated *m* times) are created. The imputed missing values are sampled from their predictive distributions based on observed data. Thus multiple imputation is based on a Bayesian approach.[141] The imputation procedure must fully account for all uncertainty in predicting missing values by injecting appropriate variability into the multiple imputed values.

Standard statistical methods (e.g., logistic regression) are then used to fit the model of interest to each of the imputed datasets.[60] The estimated associations for each of the imputed dataset will differ because of the variation introduced in the imputation of the missing values. The imputed datasets are only useful when they are averaged together to give an overall estimated association.[141] Standard errors are calculated using Rubin's rules, which takes into account the variability in the results between the imputed datasets, reflecting the uncertainty associated with the missing values.[73,94]

In this thesis, the multivariate normal distribution method, the Markov Chain Monte Carlo multiple imputation procedure was used to handle missing data. This procedure assumes that all variables in the imputation model have a joint multivariate normal distribution.[73] The Markov Chain Monte Carlo algorithm fills in missing data by drawing from a conditional distribution, in this case, a multivariate normal distribution, of the missing data given the observed data.[73] In simulation studies, multivariate normal distribution methods lead to reliable estimates even when the normality assumption is violated given sufficient sample size (e.g., reliable for both categorical and measured variables).[73] However, biased estimates have been observed when working with small sample sizes, and when the percentage of missing data is high.[73]

CHAPTER 2: Preoperative predictors of acute postoperative pain control: a systematic review and meta-analysis[153]

Abstract

Objectives

Inadequate postoperative pain control is common and is associated with poor clinical outcomes. This study aimed to identify preoperative predictors of poor postoperative pain control in adults undergoing inpatient surgery.

Design

Systematic review and meta-analysis.

Data Sources

MEDLINE, EMBASE, CINAHL, and PsychInfo were searched through October 2017.

Eligibility Criteria

Studies in any language were included if they evaluated postoperative pain using a validated instrument in adults (≥18 years) and reported a measure of association between poor postoperative pain control (defined by study authors) and at least one preoperative predictor during the hospital stay.

Data extraction and synthesis

Two reviewers screened articles, extracted data, and assessed study quality. Measures of association for each preoperative predictor were pooled using random effects models.

Results

Thirty-three studies representing 53,362 patients were included in this review. Significant preoperative predictors of poor postoperative pain control included younger age (OR 1.18 [95%CI 1.05-1.32], number of studies, n=14), female sex (OR 1.29 [95%CI 1.17-1.43], n=20), smoking (OR 1.33 [95%CI 1.09-1.61], n=9), history of depressive symptoms (OR 1.71 [95%CI 1.32-2.22], n=8), history of anxiety symptoms (OR 1.22 [95%CI 1.09-1.36], n=10), sleep difficulties (OR 2.32 [95%CI 1.46-3.69], n=2), higher BMI (OR 1.02 [95%CI 1.01-1.03], n=2), presence of preoperative pain (OR 1.21 [95%CI 1.10-1.32], n=13), and use of preoperative analgesia (OR 1.54 [95%CI 1.18-2.03], n=6). Pain catastrophizing, ASA status, chronic pain, marital status, socioeconomic status, education, surgical history, preoperative pressure pain tolerance, and orthopedic surgery (vs. abdominal surgery) were not associated with an increased odds of poor pain control. Study quality was generally high, although appropriate blinding of predictor during outcome ascertainment was often limited.

Conclusions

Nine predictors of poor postoperative pain control were identified. These should be recognized as potentially important factors when developing discipline specific clinical-care pathways to improve pain outcomes and to guide future surgical pain research.

Introduction

Since 1999, when the Joint Commission on Accreditation of Healthcare Organizations set the standard for the appropriate assessment and management of pain, pain has been recognized as the fifth vital sign.[21] With the aging and growing population, the number of surgeries has increased to an excess of 280 million procedures performed globally every year.[33,47,91,102,139,151,152] Numerous studies suggest poor acute postoperative pain control is common and often inadequately treated.[27,79,122,137] Importantly, ineffective postoperative pain control is associated with poor outcomes including increased length-of-stay, sleep disturbance, prolonged time to first mobilization, and increased opioid use.[27,119,140] Further, poor postoperative pain control is associated with delirium in the elderly, development of chronic pain syndromes, cardiopulmonary, and thromboembolic complications.[27,83,100,118,122] Postoperative pain may be improved by understanding the preoperative predictors of poor pain control by allowing use of anticipatory and individualized treatments.[126,156]

A previous systematic review reported a limited number of predictors of poor postoperative pain control including age, anxiety, preoperative pain, and surgery type.[75] However, quantitative analysis was not possible due to variability in the reporting of measures of associations and study design heterogeneity of the included studies. Since its publication nearly a decade ago, many additional studies have been published with improved methodological rigour,[58,85,98,110] thus providing a new opportunity to provide an updated summary of the literature and to generate pooled estimates of risk. The goal of this study was to systematically identify significant preoperative predictors of poorly controlled acute postoperative pain and to quantify the

associated risks. We focused on acute postoperative pain experienced during the surgical hospitalization. This meta-analysis is important to help identify predictors that could inform future surgical pain research and aid in the development of discipline-specific clinical care pathways (e.g., enhanced recovery after surgery programs) to improve pain outcomes.

Methods

This review was reported according to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) standards for systematic reviews and meta-analyses of observational studies. This review was also conducted based on an *a priori* protocol registered with PROSPERO International Prospective Register of Systematic Review (ID: CRD42017080682, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080682).[97,134,145]

Patient and Public Involvement

Patients and the public were not involved in the development of this systematic review.

Search Strategy

A search strategy was developed using the *Peer Review of Electronic Search Strategy* (PRESS)[103] in consultation with two research librarians. We focused on the keywords "pain", "pain measurement", "surgery", and "predictors". We searched MEDLINE (1950-October 13th, 2017), EMBASE (1980-October 13th, 2017), CINAHL (1937-October 13th, 2017) and PsychInfo (1967-October 13th, 2017) (Appendix S1, online supplemental information). To maximize sensitivity for studies of prognosis, search filters were not used, and no restrictions were placed on date or language of publication.[8,45] Our search was repeated using Google and Google Scholar

for the grey literature. Bibliographies of included studies were searched by hand for other relevant articles. A local pain specialist was also consulted to identify any potential ongoing studies or unpublished data.

Study Inclusion

We included observational studies (cohort and cross-sectional) reporting on adults (≥18 years old) undergoing surgery and admitted for at least 24 hours following their procedure (e.g., excluded ambulatory surgery/procedures, dental procedures, carpal tunnel release, etc.), and studies that assessed for the association between preoperative patient-level predictors and poor postoperative pain control (as defined by individual study authors). Only inpatient procedures were included to minimize the heterogeneity of the surgical population as well as providing more reliable pain outcomes. Perioperative predictors were not assessed because our primary aim was to inform clinicians evaluating patients in the preoperative clinical setting where perioperative risk factors may not be known or modifiable. No interventional studies were included.

Studies were required to report an assessment of pain during the inpatient period using a validated pain scale. Previous studies have demonstrated that the visual analogue scale (VAS), numeric rating scale (NRS), and verbal rating scales (VRS) for pain are highly correlated with each other, and thus they were considered comparable in the present study.[84] To facilitate pooling of data, we only included studies that reported a measure of association, such as an odds ratio (OR) or relative risk (RR), as well as studies with raw data where an OR could be manually calculated. Conference abstracts, reviews, protocols, and secondary publications (of studies already included in our review) were excluded. Two reviewers (M.Y. and R.H.) independently

reviewed titles, abstracts, and full-text articles of the retrieved studies in duplicate. Discrepancies were resolved by consensus. Inter-rater agreement was evaluated using Cohen's κ statistic for the full-text review stage.

Data Extraction

Study information such as author, year and country of publication, sample size, pain scale used, the definition of poorly controlled postoperative pain, number of predictors adjusted for in a multivariable regression model (where applicable), and the average age of the sample population were extracted. Both unadjusted and most adjusted effect estimates were recorded whenever multiple estimates were presented. For studies that reported their results in distinct strata (e.g., young vs. old age, or moderate vs. severe pain), each stratum was treated as an independent study for the pooled analysis (no patients were analyzed in duplicate).[76,98,117,125] Non-English studies were data-extracted with the help of a translator.

Study Quality Assessment

We used a component-based approach to assess the quality of included studies.[67] The following variables were considered to be the most important quality indicators for studies of prognosis (definition of quality indicators are in Table S1, online supplemental information)[67]: description of population, non-biased selection, adequate follow-up (e.g., postoperative pain measurements were recorded for at least 80% of study participants), predictor measurement, outcome measurement and ascertainment, adjustment for confounding variables (operationalized as adjusting for at least 3 potential confounders), precision of reported results (e.g., reporting of confidence intervals), as well as the use of an appropriate reference standard (e.g., definition of

poor postoperative pain control provided).[8,67,92] Data-extraction and assessment of study quality were performed in duplicate; discrepancies were resolved by consensus. If a study presented unclear data, the corresponding author was emailed with a follow-up email after two weeks if a response was not received.

Statistical Analysis

We used ORs as the common measure of association. RRs were converted to odds ratio using the formula, $OR = RR/(1/[1/(1-P_o)]+P_o)$, where P_o is the incidence of the outcome of interest in the non-exposed group.[154] When raw data were presented, ORs were manually calculated. For the primary analysis, the most adjusted ORs were used to determine the pooled estimates. The analysis was then repeated using the least adjusted effect estimates. Pooled estimates, expressed as ORs (with 95% confidence intervals [CI]), were determined for each preoperative predictor associated with poor postoperative pain control levels using the DerSimonian and Laird random effects model and visualized using forest plots. A random effects model was chosen due to the variability in surgical specialties, definitions of poor postoperative pain, and the reported timing of postoperative pain assessment in the included studies. Meta-analysis was performed using the 'metan' command within STATA v.15 (StataCorp, College Station, Texas). Level of significance was set at $\alpha=0.05$.

Between-study heterogeneity was examined and quantified using the Cochran Q test and I^2 statistic.[72] Stratified analysis and meta-regression were performed to explore for potential sources of heterogeneity based on an *a priori* list of factors related to study quality and clinical prognosis. Stratification was conducted on the following variables: degree of statistical

adjustment (e.g., operationalized as adjustment for <3 vs. ≥3 variables), definition of poor postoperative pain control (moderate vs. severe pain; moderate pain: 3-6, severe pain: >6 on an 11-point scale; studies not using a numeric scale (e.g., morphine requirements as the definition for poor pain control) were considered moderate pain), surgical discipline, blinding of predictors when assessing pain scores, and location of pain assessment (e.g., post-anesthetic care unit vs. ward). Preoperative factors only reported in a single study could not be pooled and therefore were not included in the final analyses. We did not assess for publication bias because conventional tools used to examine for publication bias, such as funnel plots, are intended to detect small study effects. Small study effects are challenging to interpret for meta-analyses of observational studies, such as ours, where multiple sources of heterogeneity may be present, such as those arising from true clinical differences (e.g., different surgical disciplines/procedures) or bias inherent to individual studies (e.g., residual confounding, lack of blinding).[45]

Results

Literature Search & Study Characteristics

We identified 9,753 articles through electronic database and grey literature search (Figure 1). Consultation with a pain expert and searching of the grey literature yielded 38 articles. After initial screening, 291 articles were included for full-text review. Full-text review resulted in the inclusion of 33 articles for data extraction with excellent inter-rater reliability (κ= 0.83 [95%CI 0.71-0.91]). No unpublished studies were identified and included in the final analysis.

The 33 included studies represented 53,362 patients with publication dates ranging between 2002 and 2017 (study characteristics of included studies are in Table

1).[9,15,17,18,22,28,44,52,53,58,76,77,85,88,95,98,99,101,105,108,110,111,117,120,123,125-127,130,138,144,147,155] Twenty-six studies were prospective cohort studies (79%) and 7 were retrospective cohort studies (21%). Most studies were conducted in Europe (17/33 studies, 51.5%), followed by Asia (8/33 studies, 24.2%). Studies involving a mixture of specialties (11/33 studies, 33.3%) and general surgery (10/33 studies, 30.3%) had the largest representation. A variety of thresholds were used to define poor pain control on a standard 11-point scale (0-10) across studies; the most common definition of significant postoperative pain was ≥4 out of 10 (13/33 studies, 39.4%) followed by > or ≥ 5 out of 10 (7/33 studies, 21.1%). NRS, VAS and VRS scale for pain was used in 57.6%, 42.4%, and 3.0% of studies respectively. The most common time-interval when postoperative pain was measured was between 24-48 hours (19/33 studies, 57.6%). The mean number of predictors (including preoperative and perioperative variables) explored per study was 10.0 (SD: 5.73, range 1-19) (Table 1). There was a lack of dedicated prognostic studies evaluating predictors of postoperative pain control in most surgical sub-specialities including neurosurgery, spine surgery, otolaryngology and plastic surgery.

Assessment of Study Quality

The overall methodological quality of the included studies was generally high except for the use of a blinded outcome assessment (Figure 2). In 25 studies (76%), there was either no blinding or no reporting on whether there was blinding of predictors during outcome ascertainment. The lack of blinding of predictors during outcome ascertainment in the majority of studies could lead to increased risk of misclassification bias. Twelve studies (36%) did not adjust for at least 3 potential confounders, 5 studies (15%) did not provide definitions of preoperative predictors, and 4 studies (12%) did not define how their sample was selected.

Preoperative Predictors of Poor Postoperative Pain Control

Of the 23 variables examined, 9 statistically significant preoperative predictors of poor postoperative pain control were found: younger age (OR 1.18 [95% CI 1.05-1.32]), female sex (OR 1.29 [95% CI 1.17-1.43]), smoking (OR 1.33 [95% CI 1.09-1.61]), history of depressive symptoms (OR 1.71 [95% CI 1.32-2.22]), history of anxiety symptoms (OR 1.22 [95% CI 1.09-1.36)], sleep difficulties (OR 2.32 [95% CI 1.46-3.69]), higher BMI as a continuous variable (OR 1.02 [95% CI 1.01-1.03]), presence of preoperative pain (OR 1.21 [95% CI 1.10-1.32]), and use of preoperative analgesia (OR 1.54 [95% CI 1.18-2.03]). Pooled ORs and definition for each preoperative variable are shown in Table 2. Summary forest plots of significant preoperative predictors of poor postoperative pain control are presented in Figure 3. Significant heterogeneity was detected in 5 of these predictors (female sex, younger age, the presence of preoperative pain, history of anxiety symptoms, and smoking) with I^2 values ranging from 50.4% to 82.4% (Table 2). Detailed forest plots for each significant preoperative predictor are shown in online supplemental Figures S1 to S3.

Non-Significant Preoperative Predictors of Poor Postoperative Pain Control

Fourteen predictors were not significant in the final analysis: pain catastrophizing scale (exaggerated negative perception to painful stimuli) as a dichotomous variable, marital status, high BMI as a dichotomous variable, any previous surgical history, orthopedic surgery compared to abdominal surgery, diabetes, pain catastrophizing as a continuous variable, higher education, age as a continuous variable, chronic pain, American Society of Anesthesiologists (ASA) Physical Status, alcohol use, preoperative pressure pain tolerance and low socioeconomic status

(Table 2). Detailed forest plots for each non-significant preoperative predictor are shown in online supplemental Figures S4 to S8.

Preoperative variables reported in only one study (and hence were excluded from the meta-analyses) included: patient weight, surgeon's anticipated pain level, self-assessment of good health, generalized self-efficacy scale, sedentary lifestyle, employment status, short portable mental status questionnaire, preoperative delirium (confusion assessment method), constipation, rectal volume, body image scale, history of cancer, hypertension, heart disease, preoperative anemia, anticonvulsant medication, home sedatives, electrical pain threshold, heat pain threshold, von Frey pain intensity, blood type, preoperative 24 hour urinary cortisol level, thoracic surgery, spine surgery, head & neck surgery, and total knee replacement.

Stratified Meta-Analysis and Meta-Regression

Stratified meta-analyses (according to the level of statistical adjustment, the definition of poor pain, surgical discipline, blinding of predictors, and location of pain assessment) showed no differences in the pooled estimates and therefore did not explain the significant level of heterogeneity observed between studies. These results were corroborated by meta-regression. Repeating the analysis using least adjusted versus most adjusted models also found similar pooled results for each preoperative predictor.

Discussion

In this systematic review and meta-analysis of 33 studies, we identified 9 preoperative predictors that were negatively associated with pain control after surgery: young age, female sex, smoking,

history of depressive symptoms, history of anxiety symptoms, sleep difficulties, higher BMI, presence of preoperative pain, and use of preoperative analgesia. The most well-studied predictors were female sex (number of studies, n=20), young age (n=14), and the presence of preoperative pain (n=13). The strongest negative prognostic factors were a history of sleeping difficulties (number of studies, n=2) and depression (n=8), which were independently associated with approximately 2-fold higher odds of poor postoperative pain control. Our findings are consistent with and extend the results of the previous systematic review by Ip and colleagues.[75] In addition to the predictors previously described, we identified 6 additional preoperative predictors of poor postoperative pain control.[75]

Previous reports have been inconsistent in their conclusions regarding the association of female sex with worse pain prognosis after surgery.[75,138] Some have observed higher pain scores in females,[53,95,105,108] whereas others failed to find such a difference between sexes.[123,125,130] In this meta-analysis, we found females had an approximately 30% increased odds of poor postoperative pain control compared to males. Sex differences may potentially relate to complex psychosocial and biological factors, such as an increased willingness of women to communicate pain,[16] and subjective differences in pain perception and experience.[75] Indeed, females are reported to require 11% greater doses of morphine on average compared to males in order to achieve adequate postoperative analgesia.[14] Furthermore, younger age (as a dichotomous variable) was found to be a significant predictor for poor postoperative pain control. When examined as a continuous variable, the point estimate also suggested older age was protective (e.g., for every decade of age, there was an associated 30% decrease in the odds for poor postoperative pain control), though this association was not statistically significant. Notably,

studies examining age as a continuous variable may not have been able to detect a statistically significant difference because the majority of these studies were restricted to older patients and few examined younger subjects. Further, it is possible that the association between age and postoperative pain is non-linear. While sex and age are non-modifiable risk factors, this knowledge can still be used to anticipate pain trajectories and individualize analgesia requirements in the perioperative period.

Novel risk factors identified in this study included smoking, history of depressive symptoms, preoperative analgesic use, and higher BMI. Smoking has been previously reported to be a negative prognostic factor for pain control and a predictor of increased use of opioid analgesia.[30,39] Our finding implicating this modifiable risk factor in the setting of surgical pain supports the undertaking of future interventional studies evaluating the impact of preoperative smoking cessation programs on postoperative pain control. The presence of depression (whether self-reported or measured with a validated scale) was also associated with worse pain outcomes. Importantly, a wide spectrum of depression was represented by the included studies, and even included subjects with relatively mild depressive symptoms.[28] Thus even mild or moderate levels of depressive symptoms may be associated with an increased odds of poor postoperative pain control. The use of preoperative analgesia, especially opioid therapy has been linked to poor postoperative pain control in numerous studies.[81,98] This may be due to greater preoperative severity of pain, opioid-induced hyperalgesia, and central or peripheral sensitization to pre-existing nociception.[11,98] Further research on the impact of modifying these risk factors in the pre- and peri-operative period is needed to determine its effect on improving postoperative pain outcomes.

Strengths & Limitations

The strengths of our study are the comprehensive search of the literature, inclusion of 33 articles (resulting in data on more than 53,000 patients), and the ability to generate pooled estimates for a large number of prognostic factors. The inclusion and stratification by multiple surgical specialties and the diversity of geographic locations increase the generalizability of the findings. However, the findings from the present report should be interpreted in the context of the study design. First, the primary studies included in our systematic review and meta-analysis were observational in nature. As is inherent to all observational designs, residual confounding cannot be excluded. This was particularly the case for unadjusted estimates. Nonetheless, we found that the most adjusted models yielded broadly similar results to the least adjusted estimates. Further, we performed meta-analyses on studies that had appreciable heterogeneity as it pertains to definition of poor postoperative pain control (which was variably defined by individual study authors), surgical procedure/specialty, timing and instrument used for pain assessment, and threshold used to categorize continuous preoperative predictors between studies (e.g., young vs. old). Outcome heterogeneity may have been a potential source of bias if, for example, a particular predictor was associated with an increased risk of postoperative pain with one instrument (or cut-off) and a decreased risk of pain using a different instrument (or cut-off). In such cases, a pooled analysis might fail to detect either finding. Although we do not believe this issue biased our findings, future studies should attempt to standardize definitions (common data elements) to facilitate comparisons between studies. For significant predictors that were evaluated by a limited number of studies (e.g., sleep difficulty), future studies should be performed to ensure reproducibility. Finally, there was significant statistical heterogeneity

between studies, which could not be explained by stratified analysis or meta-regression based on a variety of clinical and study design factors (and the results should be interpreted with caution for surgical discipline as there were limited number of studies in each group). This heterogeneity was likely a product of important clinical differences as the included studies differed widely in surgery type and case-mix. Additional research may further define the influence of specific types of surgery on pain control.

Conclusion

In conclusion, we identified and described 9 predictors of poor postoperative pain control in patients undergoing surgery requiring hospital admission. Early identification of predictors in patients at risk of poor postoperative pain control may allow for more individualized interventions, better pain management, and decrease reliance on pain medications (particularly opioids). Increased awareness of these predictors can also aid in the development of personalized discipline-specific clinical care pathways (e.g., multimodal analgesic strategies and enhanced recovery after surgery programs) to reduce length of stay and perioperative medical complications by improving postoperative pain outcomes. In addition, there is a lack of dedicated research in certain specialties such as spine surgery, plastic surgery, and otolaryngology that should warrant further investigation. Although acute postoperative pain is common, no standard criteria exist to classify outcomes. Future work is needed to develop consensus criteria for acute postoperative pain outcomes, ideally as an international, multicenter collaborative using the Delphi method. Future prospective (observational or interventional) studies on acute postoperative pain control should consider addressing the predictors found in this review.

Tables

Table 1. Study characteristics of included studies.

Author, Year	Country of Origin	Sample Size	Incidence of Poor Post-operative Pain Control (%)	Mean Age in Years (SD)	Study Design	Setting of Pain Assessment	Pain Scale*	Definition of Poor Pain Control	Time of Assessment[d]	Specialty	Pathology	No. of Predictors Examined
Alves et al, 2013[9]	Brazil	139	Not stated	51.7 (11.8)	PCS	Ward	VAS	>30	24	GS	Breast cancer	3
Auburn et al, 2008[15]	France	342	41.5	48 (18)	PCS	PACU	VAS & NRS	Morphine >0.15mg/kg in PACU	<24 hours	Mixed	Mixed	3
Baudic et al, 2016[17]	France	100	14.0	55.2 (12.1)	PCS	Ward	BPI	≥3	48	GS	Breast cancer	9
Belii et al, 2014[18]	Moldolva	176	Not stated	Not stated	PCS	Ward	NRS	≥5	24	GS	Abdominal pathologies	3
Borges et al, 2016[22]	Brazil	1,062	78.4	25.1 (5.7)	PCS	Ward	NRS	≥5	Immediate postoperative period	Obstetric	Non-emergent cesarean section	14
Camuo et al, 2002[28]	Brazil	346	43.4	44.3 (9.6)	PCS	PACU	VAS	>30	24	GS	Abdominal pathologies	15
Duan et al, 2017[44]	China	1002	15.5	49.5 (11.6)	PCS	Ward	NRS	≥4	24	Mixed	Mixed	3
Genov et al, 2015[52]	Russia	321	Not stated	Not stated	RCS	PACU	VAS	>4	12	Mixed	Mixed	1
Gerbershagen et al, 2014[53]	Germany	22,963	24.5	55.2[a]	PCS	Ward	NRS	≥7	24	Mixed	Mixed	3
Gorkem et al, 2016[58]	Turkey	80	Not stated	29.7 (5.8)	PCS	Ward	VAS	>40	18	Obstetric	Non-emergent cesarean section	16
Jae Chul et al, 2015[76, c]	Korea	10,575	Not stated	Young: 31.8 (5.8) Old: 74.8 (4.4)	RCS	Ward	NRS	>4	48	Mixed	Mixed	5
Jasim et al, 2017[77]	Malaysia	400	Not stated	30.4 (4.8)	RCS	PACU and Ward	VAS	Not stated	12	Obstetric	Non-emergent cesarean section	7
Katz et al, 2005[85]	United States	109	54.1	58.2 (12)	PCS	Ward	NRS	≥5	48	GS	Breast cancer	17

Kim et al, 2016[88]	United Kingdom	156	42.3	64.4 (10.9)	PCS	Ward	NRS	≥5	48	GS	Gastric tumors (endoscopic resection)	11
Lesin et al, 2016[95]	Croatia	226	19.9	67 (13)	PCS	Ward	NRS	≥5	6	Ophtho	Ophthalmologic pathologies	19
Liu et al, 2012[98, c]	United States	897	At rest: 22.4 Movement: 39.0	67 (11)	RCS[e]	Ward	NRS at rest & with activity	>4	24	Orthopedic	Primary total hip or knee replacement	17
Lunn et al, 2013[99]	Denmark	92	39.1	Median 66 (IQR:13)	PCS	Ward	VAS (with activity)	≥60	6-24	Orthopedic	Total knee arthroplasty	4
Mamie et al, 2004[101]	Switzerland	304	25.1	45[a]	PCS	Ward	VAS	>5	24	Mixed	Abdominal and orthopedic pathologies	10
Mei et al, 2010[105]	Germany	1,736	28.5	Not stated	PCS	PACU	NRS	>4	After extubation	Mixed	Mixed	10
Murray et al, 2016[108]	South Africa	1,231	61.9	44[b]	PCS	Ward	VAS	>40	24	Mixed	Mixed	8
Nishimura et al 2017[110]	Japan	64	48.4	60 (11)	PCS	Ward	VAS	>40	6-60	GS	Partial mastectomy for cancer	8
Orbach-Zinger, et al 2016[111]	Israel	245	Good sleeper: 12.8 Poor sleeper: 27.5	Good sleeper: 34.9 (4.9) Poor sleeper: 34.1 (4.9)	PCS	Ward	VRS	>7	24	Obstetric	Non-emergent cesarean section	3
Persson et al, 2017[117, c]	Sweden	152	Not stated	Median 49 (IQR: 29)	PCS	PACU	VAS	>40	1.5	GS	Laparoscopic cholecystectomy	2
Petrovic et al, 2014[120]	Serbia	90	48.9	High pain group: 64.2 (3.8), Low pain group: 69 (3.9)	PCS	Ward	NRS	≥5	12	Orthopedic	Total hip arthroplasty	15

Radinovic et al, 2014[123]	Serbia	234	Not stated	71.2 (8.3)	PCS	PACU	NRS	≥7	1	Orthopedic	Hip fractures	14
Rakel et al, 2012[125, c]	United States	215	Moderate pain: 46.0 Severe pain: 27.0	61.7 (9.8)	PCS	Ward	NRS (0-21)	8-14 (mod) 15-20 (severe)	48	Orthopedic	Total knee arthroplasty	17
Rehberg et al, 2017[126]	Switzerland	198	44.9	57.5 (12.5)	PCS	Ward	NRS	>3	24	GS	Breast cancer	15
Robleda et al, 2014[127]	Spain	127	61.0	71.0 (18)	RCS	PACU	NRS	≥4	Immediate in PACU	Orthopedic	Femur fractures and prosthetics	15
Sananslip et al, 2016[130]	Thailand	340	28.5	54.8 (17.8)	PCS	Ward	NRS	≥4	24-48	Mixed	Mixed	12
Sommer et al, 2010[138]	Netherlands	1,300	30.2	56 (15.5)	PCS	Ward	VAS	>40	24	Mixed	Mixed	15
Storesund et al, 2016[144]	Norway	336	67.3	52[b]	RCS[e]	PACU	VAS or vNRS	≥4	At time of transfer out of PACU	Orthopedic	Ankle fractures	15
Tighe et al, 2014[147]	United States	7,731	60.9	Female: 56.4[b] Male 56.6[b]	RCS	Ward	NRS	≥7	24	Mixed	Mixed	1
Zhao et al, 2014[155]	China	73	58.9	Median 43 (IQR:57)	PCS	PACU and Ward	VAS	>30	24	GS	Hemorrhoids	12

*Pain measured at rest, unless otherwise stated.
[a] Authors' estimate (study only included age ranges).
[b] Variance not stated.
[c] Studies which divided their dataset into two groups when evaluating predictors: Jae Chul et al: young vs old age group; Liu et al: NRS at rest vs with activity; Persson et al: female vs male; Rakel et al: moderate vs severe pain outcome.
[d] Time of assessment measured in hours.
[e] Labelled as a cross-sectional study design by study authors, but methodology more represent a retrospective cohort study design.
BPI- Brief pain index (0-10), VAS- Visual Analogue Scale for Pain (0-100mm), NRS- Numeric Rating Scale for Pain (0-10), vNRS- Verbal Numeric, Rating Scale for Pain (0-10), PACU- Post-anesthesia care unit, Mixed- more than one specialty or pathology, PCS- Prospective Cohort Study, RCS-Retrospective Cohort Study, and GS- General Surgery

Table 2. Pooled odds ratios and definitions of preoperative predictors of poor postoperative pain control.

Preoperative predictor	No. of studies included in pooled estimate	No. of patients	Odds ratio (95% CI)	p-value	I^2 statistic	Definition
Younger age	14	5,577	1.18 (1.05 to 1.32)	**<0.001**	79.7%*	Authors' cutoff (range ≤31 to <70 years)
Female sex	20	48,753	1.29 (1.17 to 1.43)	**<0.001**	71%*	Female sex
Smoking	9	15,764	1.33 (1.09 to 1.61)	**0.005**	55.8%*	Self-reported (any amount)
History of depressive symptoms	8	3,042	1.71 (1.32 to 2.21)	**0.018**	12.6%	Self-reported, any use of antidepressants or at least moderate score on depression scale (Hamilton Depression Rating Scale ≥19, Montgomery-Asberg Depression Rating Scale >13, Geriatric Depression Scale >6)
History of anxiety symptoms	10	2,598	1.22 (1.09 to 1.36)	**0.001**	82.4%*	Self-reported or moderate to severe score on anxiety scale (State Anxiety Inventory ≥30 to >46, Hamilton Anxiety Scale ≥25, Numeric Rating Scale for Anxiety ≥5)
Sleep difficulty	2	549	2.32 (1.46 to 3.69)	**<0.001**	0%	Self-reported chronic sleep difficulties or score >5 on the Pittsburg Sleep Quality Index
BMI (continuous)	2	1,095	1.02 (1.01 to 1.03)	**<0.001**	0%	BMI as a continuous variable
Presence of preoperative pain	13	4,733	1.21 (1.10-1.32)	**<0.001**	50.4%*	Self-reported, any preoperative pain
Preoperative analgesia use	6	2,448	1.54 (1.18 to 2.03)	**0.002**	44.0%	Self-reported use of preoperative analgesia or opioids
Age (continuous)	9	26,846	0.97 (0.93 to 1.01)	0.16	93.5%*	Age as a continuous variable
Higher education	8	2,272	0.97 (0.69 to 1.38)	0.89	43.4%	Authors' cutoff from self-reported levels of education (range: >9 years of education to college or postgraduate degree)
History of surgery	8	3,954	1.15 (0.97 to 1.37)	0.10	33.9%	Any self-reported previous surgical history
Alcohol use	5	3,851	0.89 (0.72 to 1.11)	0.29	26.2%	Self-reported alcohol use (range from any to dependence)
Low ASA physical status	5	3,629	0.94 (0.59 to 1.51)	0.80	79.0%*	ASA I compared to II or III

High BMI (dichotomous)	5	1,926	1.23 (0.98 to 1.55)	0.069	66.5%*	Authors' cutoff (range from >30 to >40 kg/m^2)
Chronic pain	4	1,583	0.96 (0.65 to 1.42)	0.84	59.5%	Self-reported chronic pain
Diabetes	4	1,287	1.02 (0.73 to 1.42)	0.90	0%	Self-reported history of diabetes
Pain catastrophizing scale (continuous)	4	407	1.02 (0.98 to 1.05)	0.37	64.8%*	Pain Catastrophizing Scale scores as a continuous variable
Marital status	3	1,571	1.42 (0.62 to 3.23)	0.41	60.1%	Self-reported as single or not married
Orthopedic procedure	3	10,879	1.06 (0.72 to 1.57)	0.77	76.3%*	Orthopedic procedure compared to abdominal surgery
Preoperative pressure pain tolerance	3	536	0.85 (0.69 to 1.06)	0.14	81.0%*	Preoperative pressure pain tolerance as measured by Wagner Force Ten Digital Force Gage FPX 50 or hand-held pressure algometer (Somedic AB, Farsta, Sweden).
Low socioeconomic status	2	1,288	0.85 (0.49 to 1.47)	0.56	0%	Brazilian Economic Classification Criteria Classes D or E or monthly family net income less than 750 US dollars
Pain catastrophizing scale (dichotomous)	2	1,476	1.47 (0.67 to 3.22)	0.34	73.0%	Authors' cutoff (range from ≥ or >15)

*significant Cochran Q test ($p<0.05$)
BMI- body mass index (kg/m^2)
ASA- American Society of Anesthesiologist
CI- confidence interval

Figures

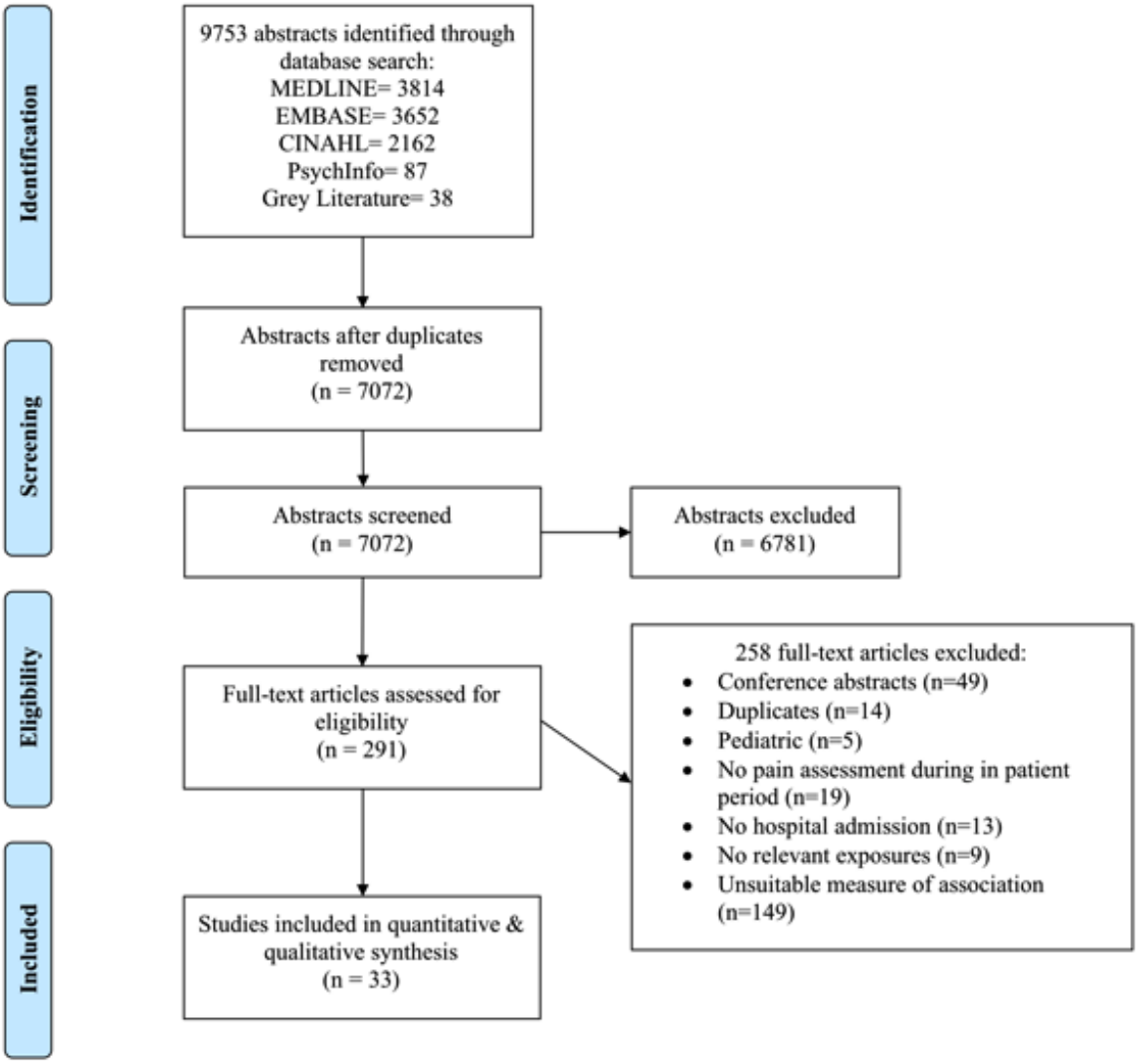


Figure 1. Systematic Review & Meta-Analysis Flow Diagram. All database and grey literature search was performed on October 13th, 2017.

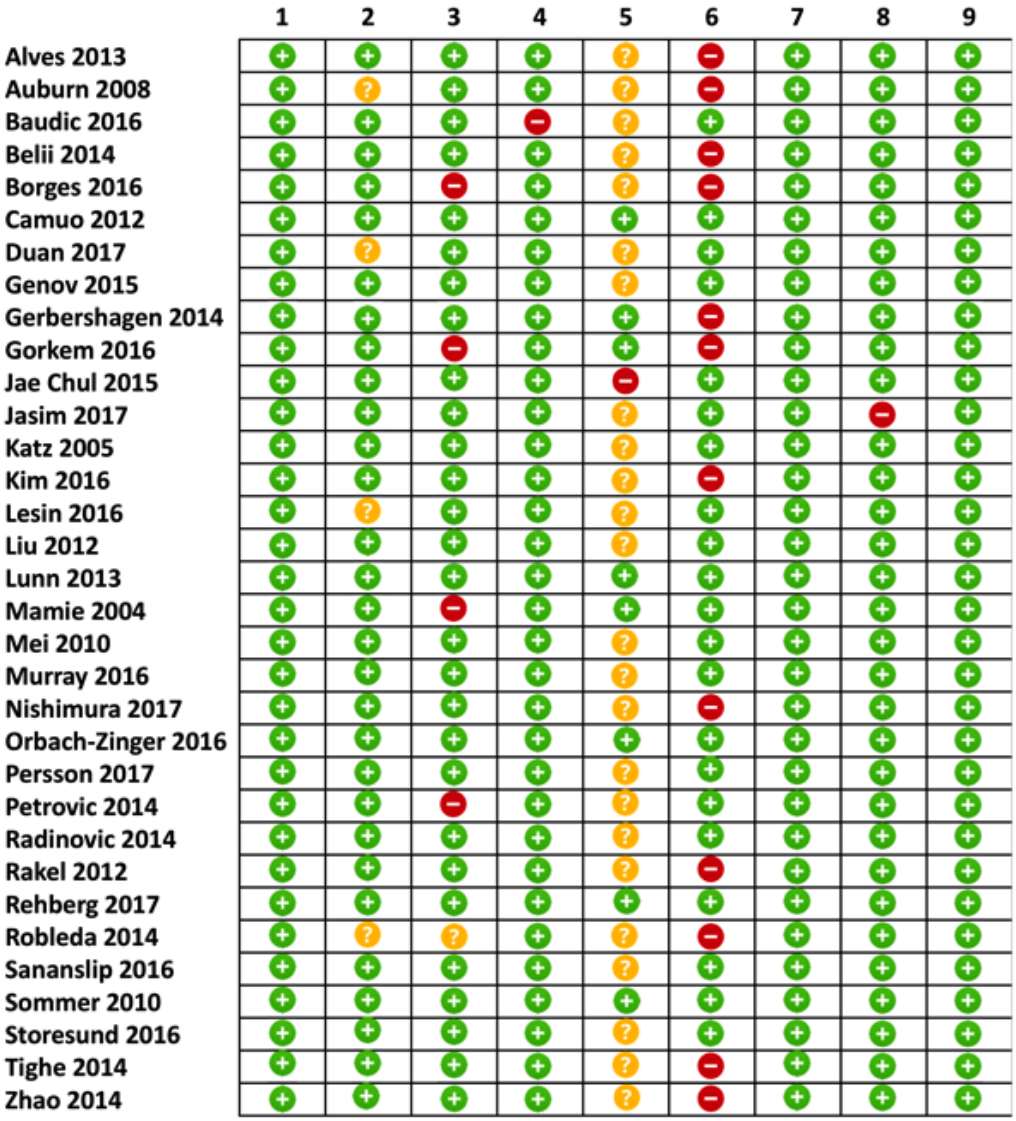


Figure 2. Assessment of study quality. 1: adequate description of population, 2: non-biased selection, 3: adequate predictor measurement, 4: adequate outcome measurement, 5: blinded outcome assessment (to predictor), 6: adequate statistical adjustment, 7: precision of results, 8: reference standard, and 9: low loss to follow up. Green: low-risk of bias, yellow: unclear-risk of bias, red: high-risk of bias.

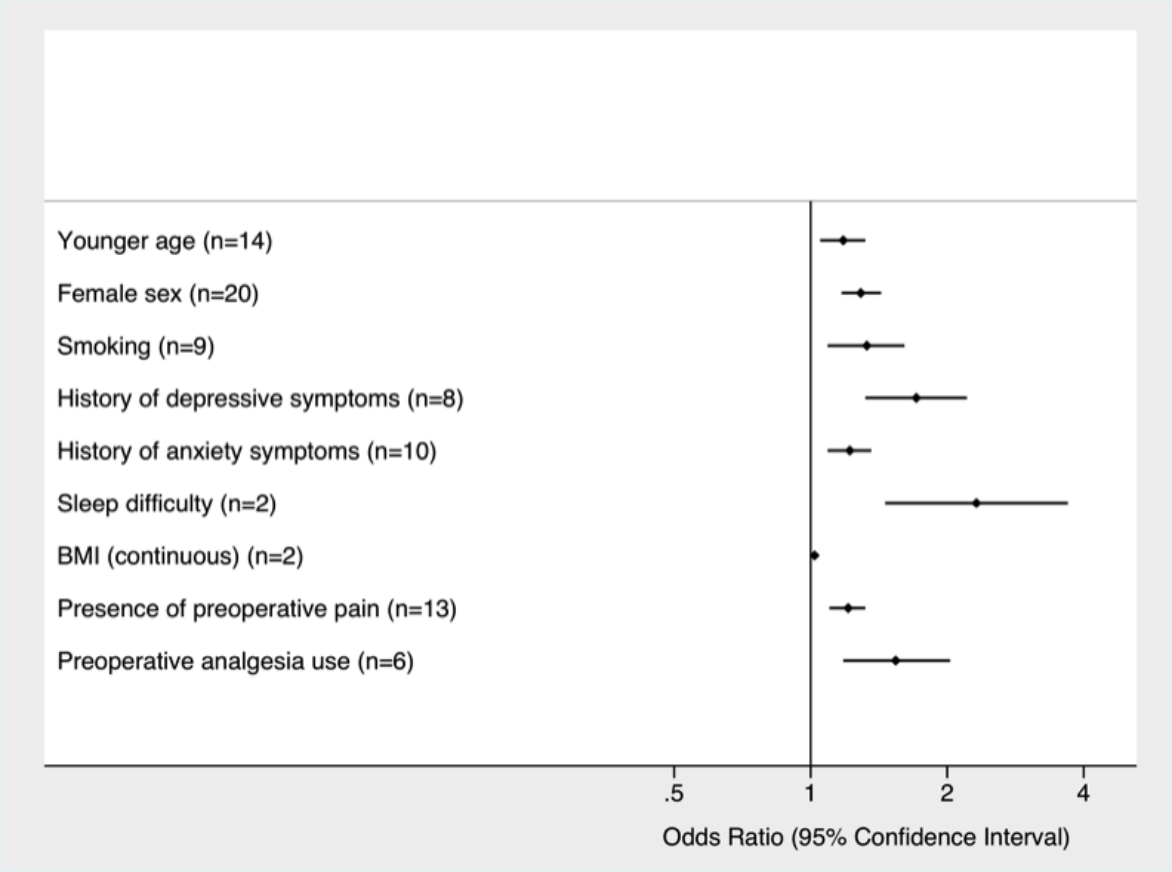


Figure 3. Summary forest plot for significant preoperative predictors of poor postoperative pain control. Odds ratios are shown with 95 percent confidence intervals. The number of studies included in the meta-analysis for each predictor is indicated.

Supplementary Tables

Table S1. Quality indicators for studies of prognosis.[67]

Quality Indicators	Description
Adequate description of population	Study described inclusion criteria for selecting patients, and when enrolled patients described demographics (at least age and sex).
Non-biased selection	Study either reported enrolling (or attempting to enroll) a consecutive series of patients meeting the inclusion criteria, or a random sample.
Low loss to follow-up	Postoperative pain measurements were available for at least 80% of patients for whom exposure data were collected.
Adequate predictor measurement	Study described reproducible and appropriate methods for measuring relevant predictors.
Adequate outcome measurement	Study utilized one of the following validated pain scales: VAS, VRS, and NRS.
Blinded outcome assessments	Study reported that outcomes were assessed by persons without knowledge of prognostic factors or that the pain outcome was determined by personnel not aware of study objectives.
Adequate statistical adjustment	Study performed statistical adjustment or controlled for at least 3 potential confounders using acceptable statistical methods.
Precision of results	Confidence intervals reported for the main outcomes of the study.
Reference standard	The study defined what was considered poor or good postoperative pain control.

VAS- visual analogue scale, VRS- verbal rating scale, NRS- numeric rating scale

Appendix S1. Database Search Strategy. Themes were combined with Boolean operator "and" and within-theme were combined with Boolean operator "or".

MEDLINE	
Pain	1. Pain, Postoperative/ 2. pain adj2 postoperati*.tw, kw 3. pain adj2 post-operati*.tw, kw 4. pain adj2 post operati*.tw, kw 5. pain adj1 operati*.tw, kw 6. post adj procedur* adj pain.tw, kw 7. surg* adj1 pain.tw,kw
Pain Measurement	1. Pain Measurement/ 2. Pain adj measurement*.tw,kw 3. Numeric adj rating adj scale.tw,kw 4. NRS.tw,kw 5. Visual adj analogue adj scale.tw,kw 6. VAS.tw,kw 7. Verbal adj rating adj scale.tw,kw 8. VRS.tw,kw
Surgery	1. EXP surgical procedures, operative/ 2. surger*.tw,kw 3. operative*.tw,kw 4. Surgical.tw,kw 5. Operation*.tw,kw
Predictors	1. predictor*.tw,kw 2. Protective factors/ or risk assessment/ or risk factors/ 3. Risk adj factor*.tw,kw 4. risk adj assessment*.tw,kw 5. protective adj factor*.tw,kw 6. Prevalence/ 7. Prevalence.tw,kw 8. Incidence/ 9. Incidence.tw,kw 10. Prognosis/ 11. Prognos*.tw,kw 12. correlati*.tw,kw
EMBASE	
Pain	1. Pain, Postoperative/ 2. Pain adj2 postoperati*.tw,kw 3. Pain adj2 post-operati*.tw,kw 4. Pain adj2 post operati*.tw,kw

	5. Pain adj1 operati*.tw,kw 6. Post adj procedur* adj pain.tw,kw 7. Surg* adj1 pain.tw,kw
Pain Measurement	1. Pain adj measurement*.tw,kw 2. Numeric adj rating adj scale.tw,kw 3. NRS.tw,kw 4. Visual adj analogue adj scale.tw,kw 5. VAS.tw,kw 6. Verbal adj rating adj scale.tw,kw 7. VRS.tw,kw 8. Exp pain assessment/ or exp pain measurement/
Surgery	1. Exp surgery/ 2. Surger*.tw,kw 3. Operative*.tw,kw 4. Operation*.tw,kw
Predictors	1. Predictor*.tw,kw 2. Risk adj factor*.tw,kw 3. Prevalence/ 4. Prevalence.tw,kw 5. Incidence/ 6. Incidence.tw,kw 7. Prognosis/ 8. Prognos*.tw,kw 9. Correlati*.tw,kw 10. "Prediction and forecasting"/ 11. risk assessment/ 12. risk factor/ 13. protective adj factor*.tw,kw 14. risk adj assessment.tw,kw
PsychInfo	
Pain	1. Pain adj2 postoperati*.tw 2. Pain adj2 post-operati*.tw 3. Pain adj2 post operati*.tw 4. Pain adj1 operati*.tw 5. Post adj procedur* adj pain.tw 6. Surg* adj1 pain.tw 7. Exp Pain
Pain Measurement	1. Pain Measurement/ 2. Pain adj measurement*.tw 3. Numeric adj rating adj scale.tw 4. NRS.tw

	5. Visual adj analogue adj scale.tw 6. VAS.tw 7. Verbal adj rating adj scale.tw 8. VRS.tw
Surgery	1. surger*.tw 2. operative*.tw 3. Surgical.tw 4. Operation*.tw 5. Exp surgery/
Predictors	1. predictor*.tw 2. Protective factors/ or risk assessment/ or risk factors/ 3. Risk adj factor*.tw 4. risk adj assessment*.tw 5. protective adj factor*.tw 6. Prevalence.tw 7. Incidence.tw 8. Prognosis/ 9. Prognos*.tw 10. correlati*.tw
CINAHL	
Pain	1. MH "postoperative pain" 2. Postoperative pain 3. Pain AND (surgery or surgical or operative or operative)"
Pain Measurement	1. MH "pain measurement" 2. Pain measurement 3. Pain assessment or pain scale or pain tool 4. Nrs or numeric rating scale 5. Vas or visual analogue scale OR visual analog scale 6. Vrs or verbral rating scale
Surgery	1. MH "surgery, operative" 2. Surgery or operation or surgical procedure
Predictors	1. MH "independent variable" 2. Predictors 3. MH "risk factors"

4. MH “risk assessment”
5. Risk factors
6. MH “prevalence”
7. Prevalence
8. Incidence
9. MH “incidence”
10. MH “prognosis”
11. Prognosis

Supplementary Figures

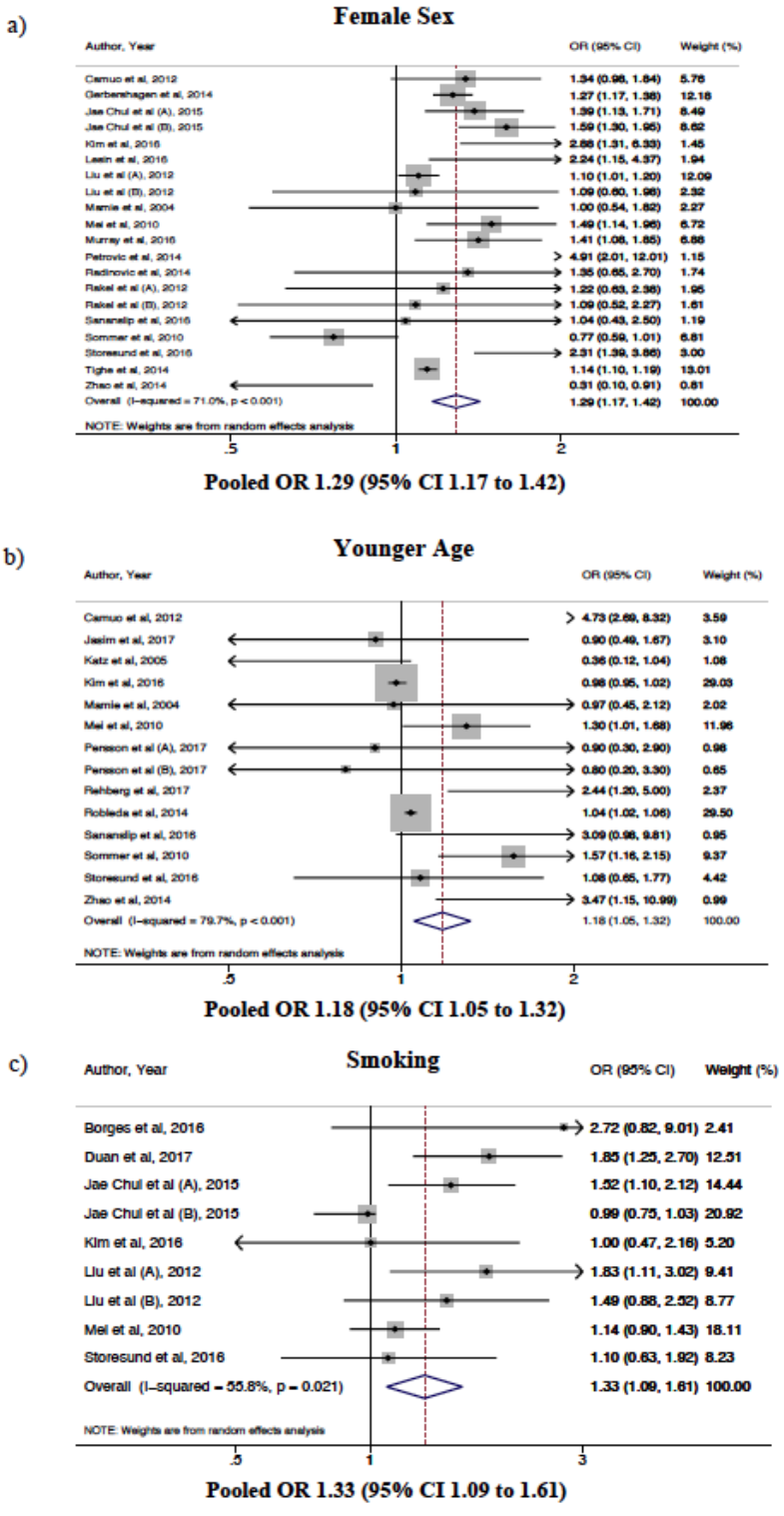


Figure S1. Forest Plot of Preoperative Predictors of Postoperative Pain. a) female sex b) younger age, and c) smoking history.

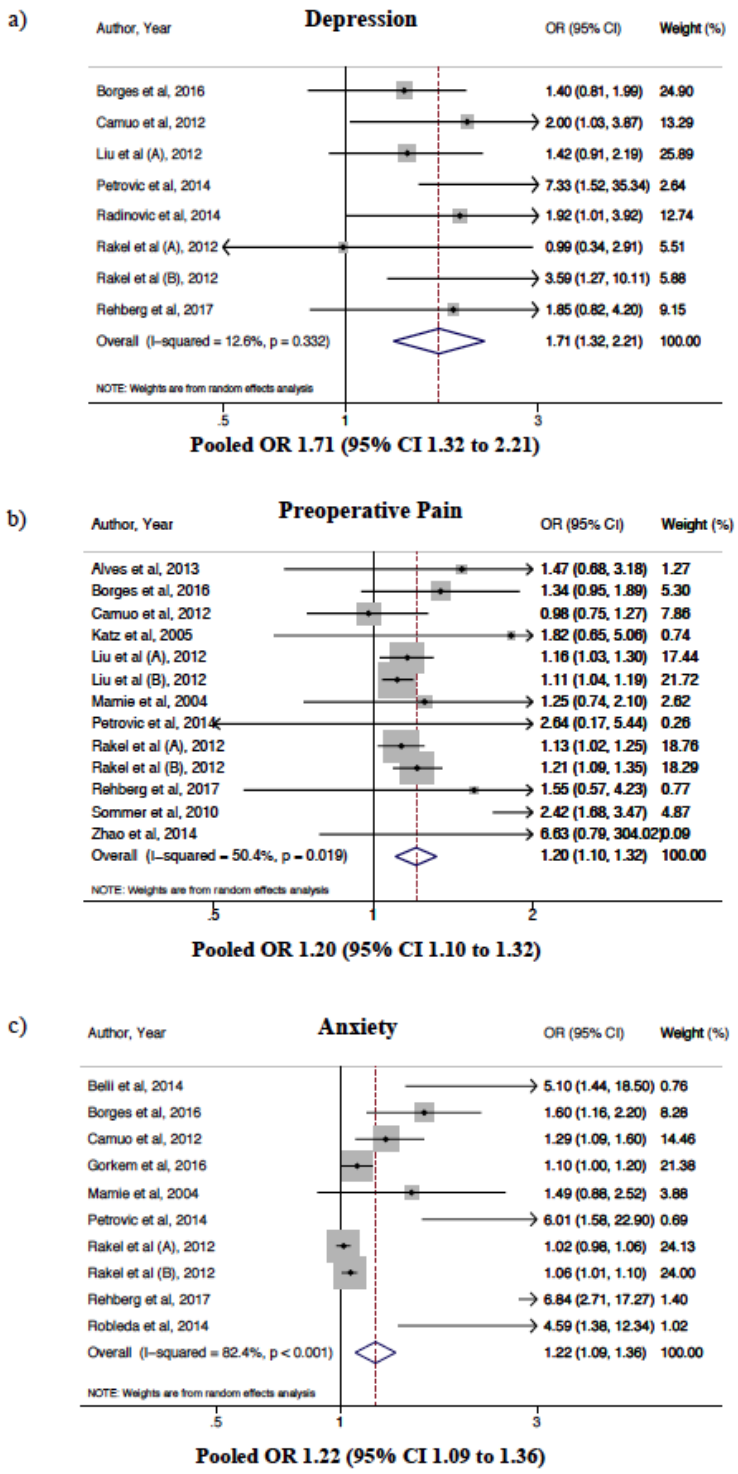


Figure S2. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) history of depression symptoms, b) presence of preoperative pain, and c) history of anxiety symptoms.

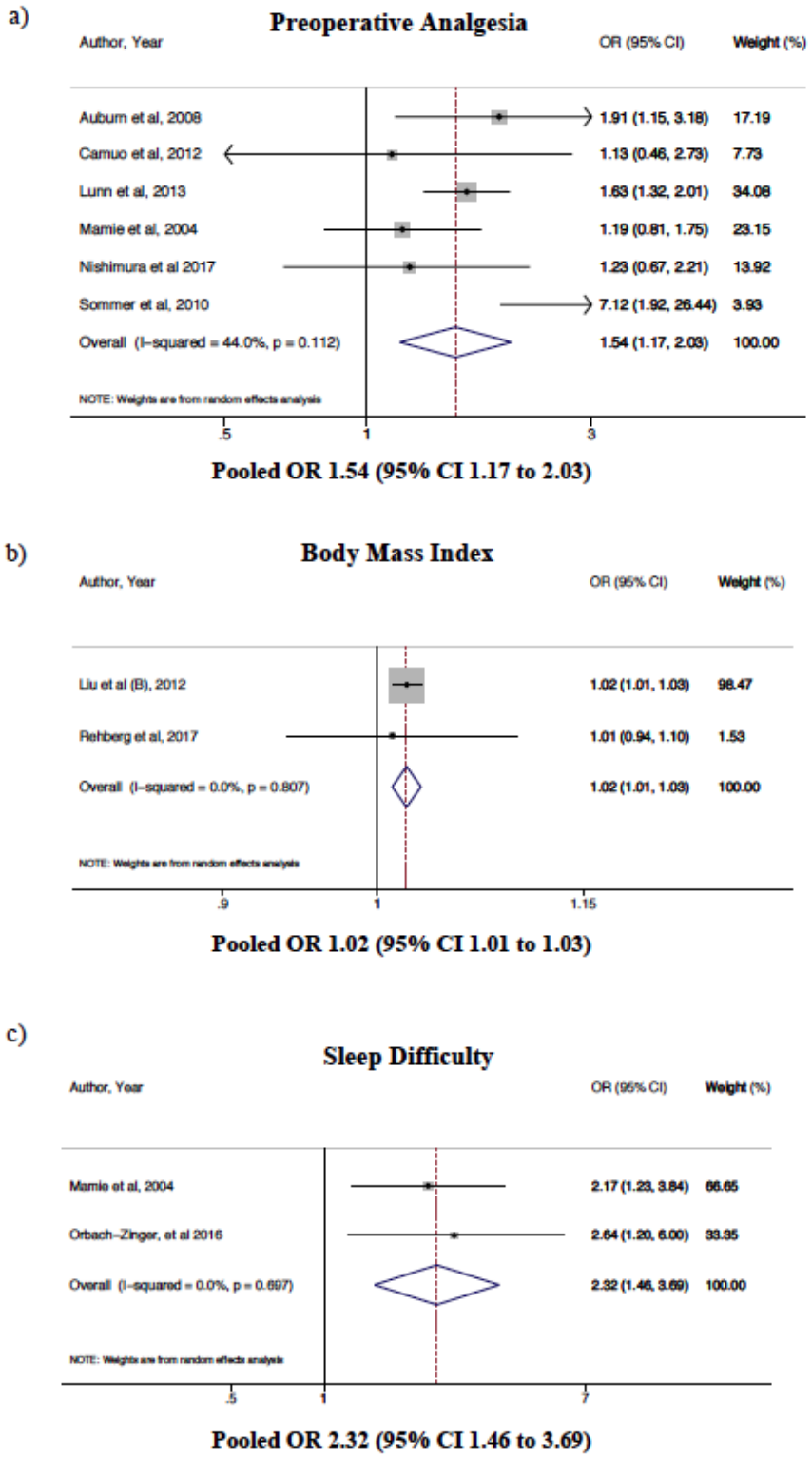
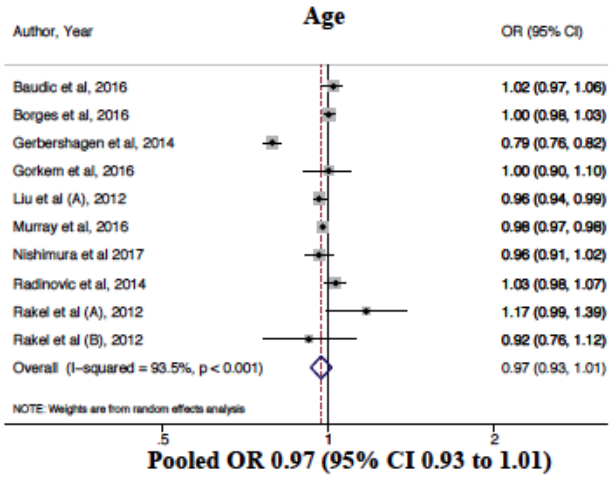


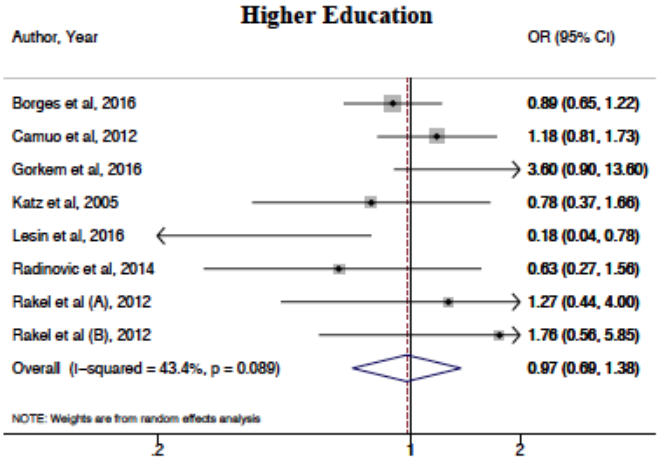
Figure S3. Forest Plot of Significant Preoperative Predictors of Postoperative Pain. a) preoperative analgesia, b) body mass index (continuous), and c) history of sleeping difficulty.

a)



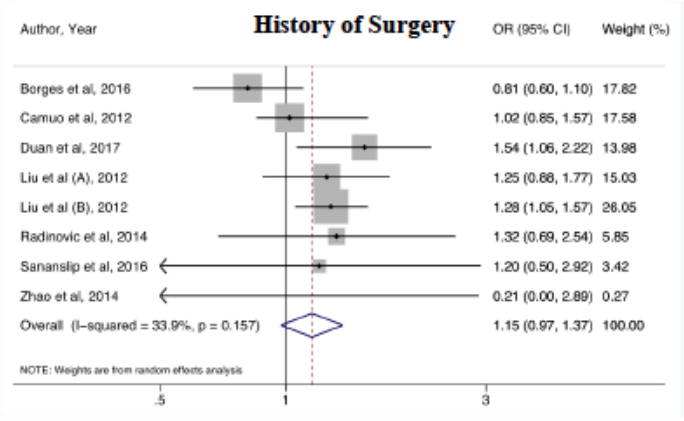
Pooled OR 0.97 (95% CI 0.93 to 1.01)

b)



Pooled OR 0.97 (95% CI 0.69 to 1.38)

c)



Pooled OR 1.15 (95% CI 0.97 to 1.37)

Figure S4. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) age (continuous), b) higher education, and c) history of surgery.

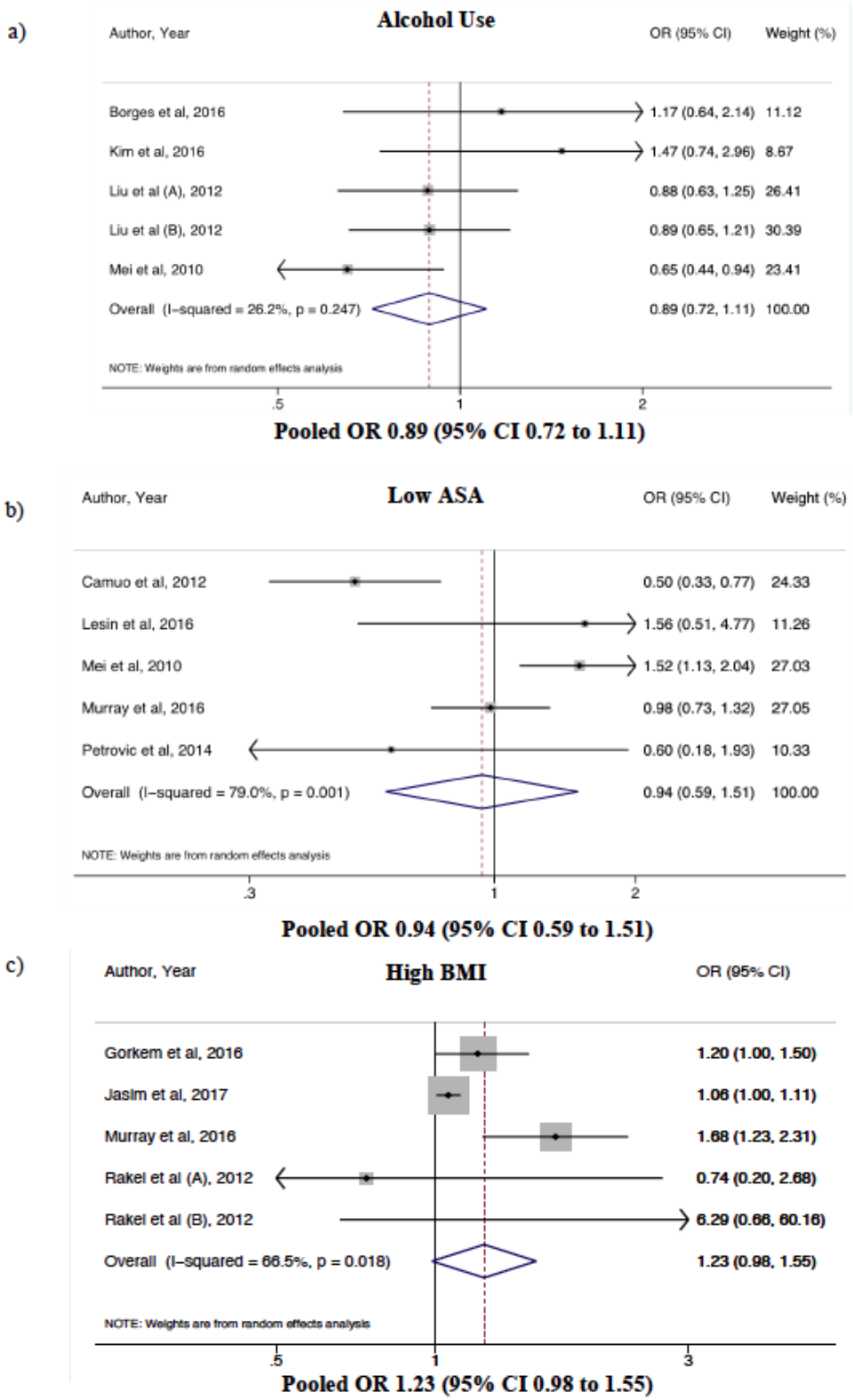


Figure S5. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) alcohol use, b) low ASA, and c) BMI (dichotomous).

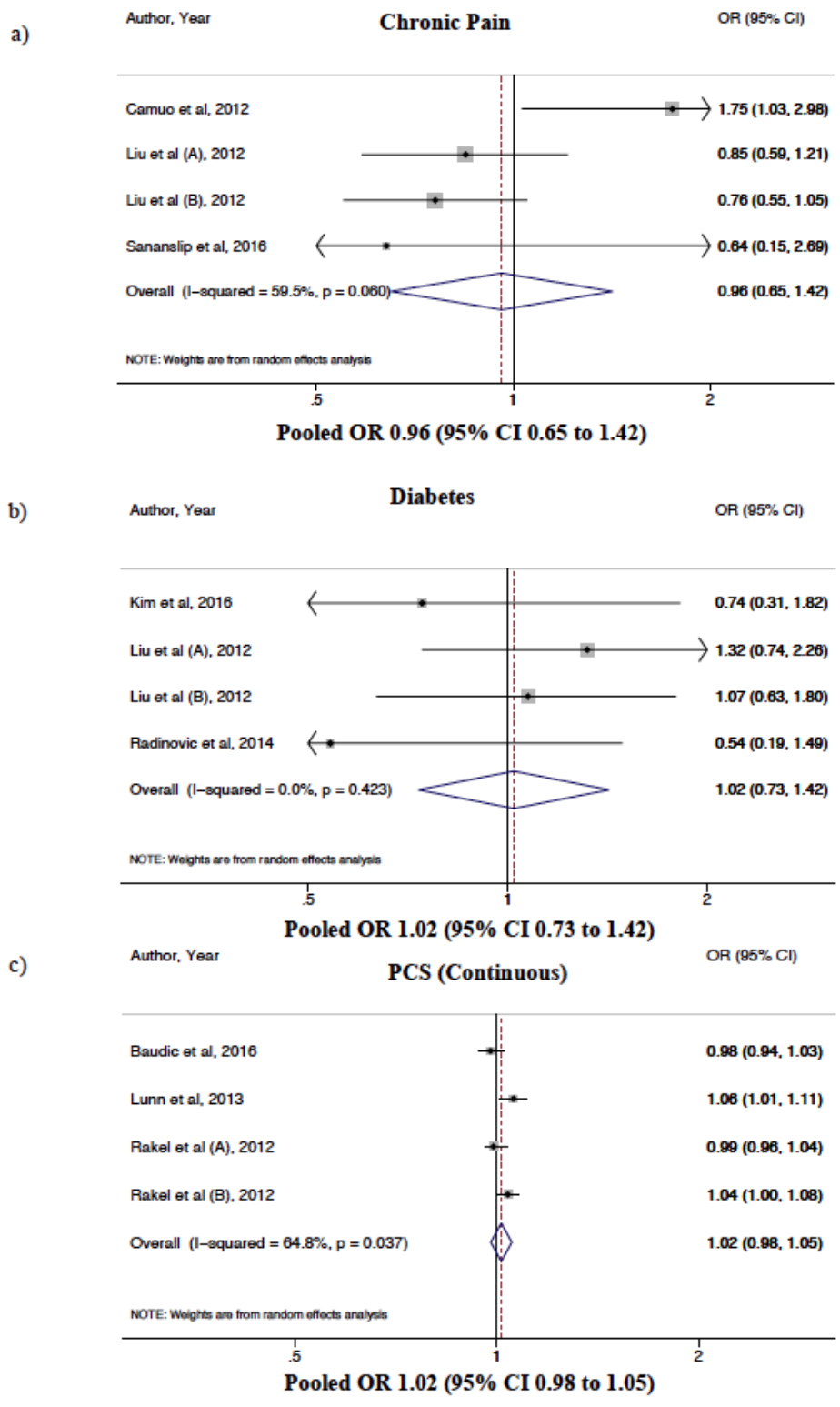


Figure S6. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) chronic pain, b) diabetes, and c) pain catastrophizing scale (continuous).

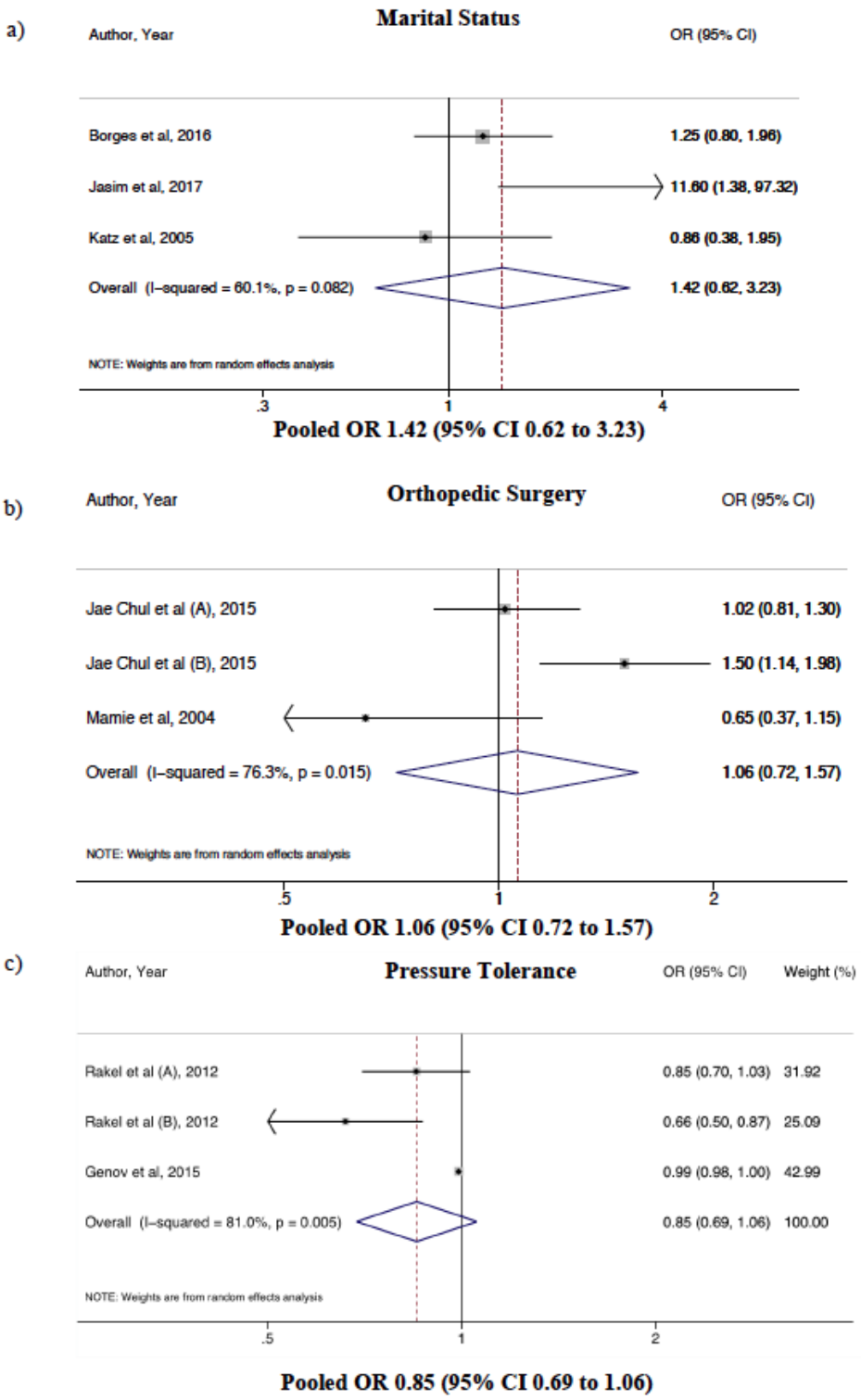


Figure S7. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) marital status, b) orthopedic surgery, and c) preoperative pressure tolerance.

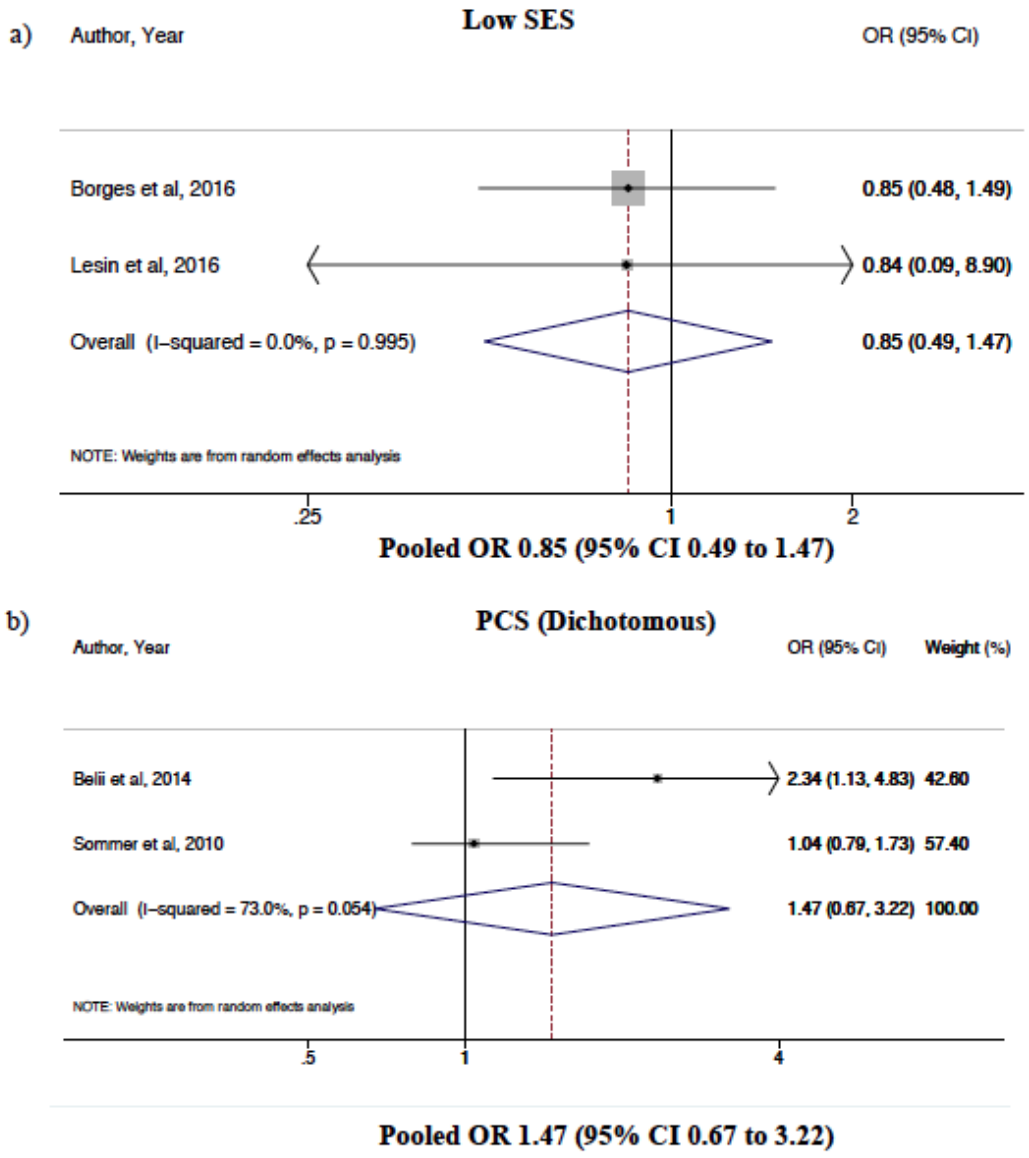


Figure S8. Forest Plot of Non-Significant Preoperative Predictors of Postoperative Pain. a) low socioeconomic status and b) pain catastrophizing scale (dichotomous).

CHAPTER 3: A Clinical Prediction Score for Poor Postoperative Pain Control After Elective Spine Surgery: the Calgary Postoperative Pain Score after Spine Surgery (CAPPS) Score

Abstract

Importance

Poorly controlled postoperative pain after spine surgery is common and can lead to patient dissatisfaction and poor outcomes. The ability to identify patients at-risk for developing poor postoperative pain control before surgery could facilitate patient education and the development of personalized clinical-care pathways to improve postoperative pain management.

Objective

Develop and internally validate a clinical prediction score for poor postoperative pain control after elective spine surgery.

Design

Single-center retrospective cohort study conducted between August 2014 and October 2017. An internal split-sample method was used to develop and validate the prediction score. Missing data was managed using multiple imputation. Multivariable logistic regression was used to derive the final model. The model's calibration and discrimination were evaluated using the Hosmer-Lemeshow goodness-of-fit test and the c-statistic, respectively.

Setting

Tertiary-care center.

Participants

Consecutive adult patients (≥18 years old) enrolled in the *Canadian Spine Outcomes and Research Network* registry who underwent elective cervical or thoracolumbar spine surgery requiring admission at the Foothills Medical Center in Calgary, Canada.

Exposures

Twenty-five candidate variables informed by a systematic review and expert consensus.

Main Outcome and Measures

Poor postoperative pain control defined by the mean numeric rating scale for pain >4 at rest in the first 24-hours after surgery.

Results

1,300 patients met eligibility criteria. Poor postoperative pain control occurred in 56.7%. Variables associated with poor pain control were younger age, female sex, daily preoperative opioid use, higher preoperative neck or back pain, higher patient health questionnaire-9 depression score, ≥3 motion segment operation, and fusion surgery. This model had a Hosmer-Lemeshow p-value of 0.99 and a concordance statistic of 0.74 (95%CI=[0.71-0.77]). Patients stratified into low-, high-, and extreme-risk groups by the prediction score had 32.0%, 63.0%, and 85.1% probability of developing poor postoperative pain control, respectively.

Conclusion and Relevance

Poorly controlled pain is common following spine surgery. This internally validated prediction score based on seven easily acquired characteristics accurately predicted the probability of developing poor pain control after spine surgery. This score can be used to develop personalized preoperative and perioperative treatment strategies to improve postoperative pain outcomes.

Introduction

Growth and increased age of our population together with improved access to diagnostic and imaging technologies has led to an increase in the number of spine operations being performed in North America.[112,124,150] The number of cervical spine procedures performed in the US between 1990 to 2000 increased two-fold.[112] Similarly, Medicare spending for inpatient thoracolumbar surgery had doubled over a 10-year period to 1 billion US dollars.[150]

Poor pain control after surgery may lead to patient dissatisfaction, delayed recovery, excessive postoperative opioid use, and prolonged hospital stay.[53] Furthermore, poor pain control has been associated with complications such as the development of chronic pain syndromes, thromboembolic diseases, and delirium in the elderly.[53,83,100] It is estimated that the economic burden of treating chronic pain that develops following acute pain in a 30-year-old individual over a lifetime is as much as $1 million.[12,37] Thus, prevention and effective relief of acute pain may improve clinical outcomes, save health-care resources, and improve quality-of-life.

Several efforts have been made to improve postoperative pain management by implementation of practice guidelines for postoperative pain management, use of pre-emptive analgesia, and increased availability of acute pain service teams.[32,132] Despite these efforts, 30-64% of patients continue to report poorly controlled pain after spine surgery.[137]

This undesirable situation may in part be a result of a lack of understanding of the patient variables that increase the risk of experiencing poor pain control after spine surgery.[153] The identification of at-risk patients before surgery may allow the implementation of anticipatory and

personalized treatment strategies in the preoperative and perioperative setting to improve pain. This is the first study to establish the predictors of poor postoperative pain control after elective spine surgery and to develop and internally validate a clinical prediction score to aid clinicians in risk-stratifying patients in the preoperative setting.

Methods

This study was conducted and reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement.[35,107] Ethics approval for this study was obtained through the University of Calgary's Conjoint Health Research Ethics Board (REB17-2096).

Study Population

Patients were consecutively enrolled through the hospital-based prospective *Canadian Spine Outcomes and Research Network* (CSORN) spine registry between August 28th, 2014 and October 4th, 2017 at the Foothills Medical Centre (FMC) in Calgary, Canada.[26] This tertiary-care center performs the vast majority of spine surgeries in Southern Alberta with a catchment area of over 2 million people. All candidate prognostic variables were collected prospectively through the CSORN registry which undertook quarterly audits to ensure data accuracy.

Entry Criteria

Adults (≥18 years) who underwent elective cervical or thoracolumbar spine surgery at the FMC and who required hospital admission for at least 24-hours were included. Exclusion criteria included patients who received intraoperative intrathecal or postoperative epidural analgesia

(previously shown to provide significant improvements in postoperative pain intensity compared to placebo),[41,63] admission to the intensive care unit, spine surgery for acute trauma, patients who underwent both cervical and thoracolumbar surgery concurrently, patients who underwent more than one surgery on the same day, and patients with less than two numeric rating scale for pain evaluations recorded on postoperative day 1.

Outcome

The primary outcome was poor postoperative pain control defined as the mean numeric rating scale for pain (NRS) >4 at rest in the first 24-hours after surgery (postoperative day 1).[54] The NRS, records pain intensity on a 11-point scale (where 0 indicates no pain and 10 indicates worst pain possible) and has been shown to have concurrent intra-rater, inter-rater, and predictive validity and reliability.[23,31,54,78] NRS≤4 has previously been established as the threshold for tolerable postoperative pain.[54] Conversely, patients experiencing NRS>4 after surgery has been associated with pain requiring analgesic interventions and negative pain-related interferences such as decreased mobility, sleep, and mood.[54] NRS for pain was collected by clinical care nurses without knowledge of the research objectives as part of usual patient care after surgery. The primary outcome was collected retrospectively from patient records. In order to evaluate accuracy of the abstraction process, the outcome was collected in duplicate for 100 random patients, and major errors, defined as the number of outcomes which were classified differently (mean NRS≤4 vs. NRS>4), was determined.

Variable Selection

Twenty-five preoperative prognostic variables were selected from 85 potential variables in the CSORN registry (eTable S1).[26] To facilitate variable selection, a systematic review and meta-analysis was performed that identified nine significant preoperative predictors of poor postoperative pain control across all surgical disciplines.[153] All nine variables were included with the exception of preoperative anxiety which was not captured in the registry. Seventeen additional variables that would be known in the preoperative setting were also included after consensus decision by 3 neurosurgeons, 1 neurologist, and 1 biostatistician. Variable selection was based on the following criteria: potential relevance in predicting postoperative pain control, likelihood of additional substantial prognostic information beyond what other variables provide, discrete and readily interpretable, and feasible to collect by any spine center.[51,68,135]

Sample Size

Based upon simulations of logistic regression analyses, at least 10 outcome events for each degree of freedom avoids biased regression coefficients, inaccurate variance estimates, and paradoxical associations.[115] Using a conservative estimated incidence of poor postoperative pain of 30%,[137] we determined a minimum sample size of 834 in the model development cohort was required to adequately evaluate 25 continuous or dichotomous variables.

Statistical Analysis

The overall sample (n=1300) was randomly divided (without replacement) into a model development (70%, n=910) and a model internal validation cohort (30%, n=390) using a deterministic random bit generator.

Identification of Predictors for Poor Postoperative Pain Control

Multicollinearity among variables was examined by the variance inflation factor (VIF) and indicated by a VIF value >5.[6,38] If collinear variables were detected, one of the variables was removed after expert consensus. Chi-square and student t-test were used to compare categorical and continuous variables to the primary outcome, respectively. Variables exhibiting a p-value ≤0.10 on univariable analyses were further evaluated by multivariable logistic regression. A Markov Chain Monte Carlo multiple imputation model with 20 imputations was used to manage missing data (eTable S2). The final model was derived using a backward variable selection method until all predictors exhibited a p-value of ≤0.05. Surgery site (cervical or thoracolumbar) was forced into the model to adjust for the effect of location of surgery on pain control. Apparent model performance was measured by the c-statistic for discrimination and Hosmer-Lemeshow Goodness-of-Fit test using 10 groups for calibration.

Clinical Prediction Score Development

To facilitate the development of a clinical prediction score, all significant continuous variables in the final model were dichotomized (threshold used based on clinical experience of the authors and past literature, eTable S3), and the multivariable analysis was repeated. The adjusted odds ratio (aOR) for each significant predictor was rounded to the nearest integer to establish each predictor's numeric score in the clinical prediction score.[149] Post-test odds of poor pain control, the product of the pretest probability of poor postoperative pain control and stratum-specific likelihood ratio (SSLR) was calculated for each tier of the score, and converted to the post-test predicted probability (Bayes' Theorem).[40,116] Adjacent cells with small sample sizes were grouped until all cells had ≥5 patients and the SSLRs were recalculated resulting in an eight-tier

Calgary Postoperative Pain after Spine Surgery (CAPPS) prediction score. As an alternate, for maximal clinical penetrance, a three-tier CAPPS score was also developed: low-risk (scores 0-4; SSLRs≤1), high-risk (scores 5-8; SSLRs >1 and ≤4), and extreme-risk (scores 9-13; SSLRs>4).[40,48]

Clinical Prediction Score Validation

Patients in the validation cohort were scored using the eight- and three-tier CAPPS score and the predicted probability for poor pain control was calculated for each tier. For calibration, these predicted probabilities were graphically compared to the observed probabilities in the validation cohort for each tier. Discrimination of the three-tier CAPPS was evaluated using percentage misclassification with the low-risk group as the reference group.[133]

Level of significance was alpha=0.05. All statistical analyses were performed using STATA version 15.1.

Results

1,300 of 1,740 patients met entry criteria (eFigure S1). There was no patient attrition during outcome collection. The mean age was 59.5 years and 48.5% were female (Table 1). The most common principal pathology and chief complaint were spinal stenosis (39.2%) and radiculopathy (42.2%), respectively. Poor postoperative pain control at rest (NRS>4) on postoperative day 1 was observed in 56.7% (n=738) of patients. There was no difference in the incidence of poorly controlled pain between the cervical and the thoracolumbar group (59.8% vs. 55.7%, p=0.20). Preoperative daily non-opioid and opioid medications were taken by 48.5% and 32.4% of

patients, respectively. Of the patients taking daily opioids, 96.4% had been doing so for >3 months. Sixty-one percent underwent fusion, and the mean number of levels operated was 1.9. All variables were comparable in the model development and validation cohorts (eTable S4). There was one major error in abstracting the primary outcome in 100 random patients abstracted in duplicate, suggesting a 1.0% (95%CI=[0.58-1.71%]) error rate.

Predictor Identification and Model Development

Nine-hundred and ten patients were randomly selected for the model development cohort. On univariable analyses, 17 variables were found to be significantly associated with poor pain control (NRS>4) (Table 2). Notably, variables such as body mass index, surgical approach (anterior, posterior, and anterior/posterior), revision surgery, grade 3 osteotomy or higher,[131] and minimally invasive surgery were not significantly associated with poor pain control (Table 2).

In the multivariable model, seven variables were found to be independently predictive of poor postoperative pain control: younger age in years (aOR=1.02, 95%CI=[1.01-1.03]; p=0.001), female sex (aOR=1.64, 95%CI=[1.22-2.19]; p=0.001), preoperative daily opioid medication use (aOR=2.61, 95%CI=[1.57-2.89]; p<0.001), higher preoperative neck or back pain measured by NRS (aOR=1.20, 95%CI=[1.06-1.20]; p<0.001), higher patient health questionnaire-9 (PHQ-9) depression score (aOR=1.03, 95%CI=[1.001-1.06]; p=0.039), ≥3 motion segment operation (aOR=2.17, 95%CI=[1.48-3.19]; p<0.001), and fusion surgery (aOR=2.13, 95%CI=[1.57-2.89]; p<0.001) (eTable S5).

This model demonstrated good calibration (Hosmer-Lemeshow chi-square=1.59, p-value=0.99), suggesting the predicted probability of poor pain control was not significantly different from the observed probability. The c-statistic was 0.74 (95%CI=[0.71-0.77]) indicating that the model adequately discriminated between patients with good and poor pain control (eFigure S2A).

Clinical Prediction Score

To facilitate clinical application, a clinical prediction score with 14 possible scores (0-13) was created after dichotomizing continuous variables (Table 3). No erosion of discrimination (c-statistic: 0.73 (95%CI=[0.70-0.77])) or calibration (Hosmer-Lemeshow chi-square=6.70; p-value=0.46) was found after this transformation. That prediction score was further collapsed to an eight-tier CAPPS score after adjacent cells with small sample sizes were combined. This eight-tier CAPPS score retained discrimination (c-statistic: 0.73 (95%CI=[0.69-0.76])) and calibration (Hosmer-Lemeshow chi-square=11.05, p-value=0.09) (eFigure S2B).

Bayesian statistics were then applied to develop the SSLRs and resultant predicted post-test probabilities for each of the eight tiers of the CAPPS score (Table 4). The SSLRs progressed from a low of 0.25 (95%CI=[0.16-0.37]) for scores 0-2 to 4.40 (95%CI=[2.90-6.67]) for patients with scores ≥9. Using a pretest probability of 56.5% (incidence of poor pain control in the model development cohort), the post-test predicted probability of poor pain control progressed from 24.2% for scores 0-2 to 85.1% for patients with scores ≥9. Furthermore, when the CAPPS score was streamlined into a three-tier CAPPS score for maximal clinical convenience, there was a similar stepwise increase in the predicted probability of poor pain control: 32.0% for low-risk (scores 0-4), 63.0% for high-risk (scores 5-8), and 85.1% for extreme-risk groups (scores 9-13).

Validation of Clinical Prediction Score

The validation cohort included 390 patients randomly selected from the original cohort (eTable S4). The CAPPS score's performance was assessed on this independent validation cohort. The predicted probabilities derived from both the eight-tier and three-tier CAPPS scores closely matched the probabilities of poor pain control observed in the validation cohort (Figure 1). When each patient within the validation cohort was risk-stratified using the three-tier CAPPS score, the percentage misclassification between the low- vs. high-risk was 38% (sensitivity: 73.8%, 95%CI=[66.9%-81.7]; specificity: 47.7%, 95%CI=[38.8%-56.7%]). When stratified between the low- vs. extreme-risk, the percent misclassification was 29.9% (sensitivity: 60.0%, 95%CI=[49.1%-70.2%]; specificity: 82.4%, 95%CI=[71.8%-90.3%]) suggesting good predictive ability of the prediction score.

Discussion

As clinical practice moves towards personalized medicine, there is an increasing need for reliable predictive tools to help physicians make appropriate therapeutic decisions. In this study, preoperative factors that predict poorly controlled pain after elective spine surgery were identified and integrated into the CAPPS score, the first internally validated prediction score developed for postoperative pain in any surgical discipline.

Daily use of opioid medications preoperatively was the strongest risk factor for developing poorly controlled pain, consistent with previous reports.[82,98] Although opioid medications are effective in the treatment of acute pain, their long-term (>3 months) efficacy in sustaining pain

relief, improving functional outcome, and safety as compared to non-opioid medications has not been substantiated.[25,43,90] In fact, numerous practice guidelines recommend against the initiation of long-term opioids for non-cancer chronic pain.[19,129] Preoperative opioid use has previously been associated with poorer standardized outcomes after spine surgery including Short Form-12, Oswestry Disability Index, and Neck Disability Index at 12-months follow-up.[93] In this study, 96.4% of patients who were consuming daily opioids had been taking them for >3months. This points to a significant opportunity to reduce opioid prescribing in the preoperative setting. Furthermore, preoperative opioid tapering has been shown to improve patient-reported outcomes following total joint arthroplasty,[65,66,109] as well as an improvement in depression, and anxiety; both of which are associated with worse pain postoperatively.[13,93,153]

Increasing depression scores on the PHQ-9 questionnaire and preoperative axial neck or back pain were other modifiable risk factors identified in this study. Depression has been previously associated with inadequate postoperative pain control,[153] and poor surgical outcomes across surgical disciplines.[28,136] Preoperative pain is also a previously recognized predictor for increased postoperative pain in other disciplins.[153] It has been proposed that current pain intensities, expectations of pain, and memory of pain all have a significant influence on the severity of future pain.[80] Pain catastrophizers[146] (not specifically identified in this study) may represent a large proportion of patients who report high on preoperative axial neck or back pain (NRS>7),[87] which has been associated with poor postoperative pain outcomes.[114,146] Both, preoperative depression and pain intensity may be significantly improved by psychotherapy methods such as acceptance and commitment therapy.[5] Acceptance and commitment therapy has

also been shown to be effective in improving a myriad of other mental health disorders such as anxiety, pain catastrophizing, and addictions.[3,148]

Non-modifiable risk factors that were associated with poor pain control included younger age, female sex, ≥3 motion segment operation, and fusion surgery. Both younger age and female sex has been previously associated with increased postoperative pain and higher analgesic requirements in other disciplines.[14,105,153] Surgeries involving more motion segments and fusion surgeries usually require larger incisions and more soft tissue manipulation leading to increased postoperative pain.[14,105,153] However, interestingly, minimally invasive surgery was not significantly associated with pain control status in this study. This is contradictory to numerous reports which suggest minimally invasive surgery has improved pain outcomes when compared to open surgery.[121]

Strategies to reduce acute postoperative pain is a major goal of enhanced recovery after surgery programs.[20,46] The ability for clinicians to risk-stratify patients preoperatively (using the CAPPS score developed in this study), creates an opportunity to develop anticipatory therapies and personalized clinical-care pathways. For example, patients identified as extreme-risk may be better candidates for resource-intensive therapies such as preoperative opioid tapering programs, and acceptance and commitment therapy.[5,109] On the other hand, less resource intensive therapies may be appropriate for patients identified as high-risk such as the use of pre-emptive analgesia and intraoperative intrathecal morphine injection following lumbar surgery.[32,41] The CAPPS score and the predictors identified in this study can also be used to inform patient selection, and appropriate adjustment of confounders in future pain related studies in spine surgery. In terms of

knowledge translation, the probability of poor pain control informed through this study can help frame patient education, inform expected pain control after surgery, and improve shared-decision making on personalizing preoperative and perioperative treatment strategies to improve pain outcomes. Notably, inadequate preoperative patient education has been shown to be significantly correlated with higher postoperative pain scores leading to increased length of hospital stay.[4,143] These individualized and preventative approaches to postoperative pain management should lead to a reduction in postoperative opioid utilization, recovery time, health-care costs, and improved patient satisfaction.

Limitations

Pain is a subjective experience with psychological, biological, and environmental determinants all contributing to this unpleasant experience. As such, developing a prediction rule that captures all the elements that predict pain is inherently difficult. Factors such as anxiety, pain catastrophizing, and kinesiophobia have been associated with poor postoperative pain control and were not evaluated in this study.[49,86,153] Future studies should evaluate whether these factors are important in spine surgery and revise the CAPPS score accordingly. Sampling bias during patient recruitment could not be assessed since data on patients not consenting to the CSORN registry was not available. The score developed here includes variables that are easily acquired in the preoperative setting. One variable, PHQ-9, may not be routinely gathered and may be a deterrent to adoption of this score in clinical practice. However, it is our hope that more spine clinics will adopt the practice of routinely evaluating preoperatively for the presence of depression in a quantitative manner. Our score exhibited a percentage misclassification between low- and high- or extreme-risk of 38.0% and 29.9%, respectively. Thus, approximately one-third

of patients were misclassified as expecting poor pain control when in fact they had good control, and vice-versa. This may lead to inappropriate overuse and underuse of pain mitigating treatment strategies leading to wasted health-care resources or subjecting patients to unnecessary risk. Lastly, the prediction score developed in this study was not externally validated. Future studies demonstrating adequate predictive performance in an external population should be performed before widespread adoption of this prediction rule.

Conclusion

Inadequate pain control is common following spine surgery. The internally validated CAPPS score based on seven easily acquired characteristics accurately predicted the probability of developing poor pain control after spine surgery. This score can be used to facilitate preoperative patient education and development of personalized clinical-care pathways to improve postoperative pain outcomes.

Tables

Table 1. Baseline patient characteristics (n=1300).

Characteristic	Missing Values, n (%)	Values
Age in years (mean ± SD)	0 (0)	59.5 (13.6)
Female sex (n, %)	0 (0)	630 (48.5)
Principal pathology (n, %)	0 (0)	
Disc herniation	0 (0)	172 (13.2)
Degenerative disc disease		166 (12.8)
Spinal stenosis		509 (39.2)
Spondylolisthesis		306 (23.5)
Deformity		71 (5.5)
Tumor		23 (1.8)
Others		53 (4.1)
Chief Complaint (n, %)		
Back pain	0 (0)	236 (18.2)
Neck pain		17 (1.3)
Radiculopathy		548 (42.2)
Myelopathy		180 (13.9)
Neurogenic claudication		304 (23.4)
Others		15 (1.2)
Patients with NRS>4 for pain on postoperative day 1 (%, 95% CI)	0 (0)	56.7 (54.1-59.4)
Postoperative oral morphine equivalence dose on postoperative day 1 in mg (mean ± SD)	0 (0)	135.4 (175.0)
Body mass index in kg/m^2 (mean ± SD)	0 (0)	29.2 (5.6)
Any nicotine products (n, %)	0 (0)	255 (19.6)
High school education or less (n, %)	44 (3.4)	503 (40.1)
Single (n, %)	11 (0.8)	340 (26.4)
History of spine surgery (n, %)	0 (0)	330 (25.4)
ASA physical status (n, %)		
ASA 1	0 (0)	256 (19.7)
ASA 2		777 (59.8)
ASA 3		263 (20.2)
ASA 4		4 (0.3)
Sleep difficulty (n, %)	25 (1.9)	985 (77.3)
Daily non-opioid medication (n, %)	38 (2.9)	612 (48.5)
Daily opioid medication (n, %)	78 (6.0)	396 (32.4)
Daily antidepressant medication (n, %)	106 (8.2)	291 (24.4)
Daily neuroleptic medication (n, %)	93 (7.2)	417 (34.6)
Chronic pain (n, %)	65 (5.0)	981 (79.4)
Preoperative neck or back pain measured by NRS (mean ± SD)	17 (1.3)	6.7 (2.4)

Depression on patient health questionnaire-9 (mean ± SD)	88 (6.8)	9.6 (6.3)
Severe preoperative disability on NDI or ODI* (n, %)	78 (6.0)	691 (56.6)
Surgical approach (n, %)		
Any anterior	0 (0)	311 (23.9)
Any posterior		930 (71.5)
Any anterior and posterior		59 (4.5)
Motion segments operation (n, %)		
1	0 (0)	650 (50)
2		379 (29.2)
≥3		271 (20.9)
Fusion surgery (n, %)	0 (0)	793 (61.0)
Minimally invasive surgery (n, %)	0 (0)	318 (24.5)
Revision surgery (n, %)	0 (0)	189 (14.5)
Grade 3 osteotomy or more† (n, %)	0 (0)	55 (4.2)

*Neck Disability Index ≥50 and Oswestry Disability Index >40

†At least pedicle or partial body resection

NRS- numeric rating scale, CI- confidence interval, SD- standard deviation

Table 2. Univariable analyses of the model development cohort for 25 candidate predictors (n=910).

Variables	Sample Size	Good Pain Control, NRS≤4 (n= 396)	Poor Pain Control, NRS>4 (n=514)	P-value
Age in years (mean ± SD)	910	61.9 (13.7)	58.1 (13.7)	**<0.001**
Female sex (n, %)	910	158 (39.9)	284 (55.3)	**<0.001**
Principal pathology (n, %)	910			
Disc herniation		53 (13.4)	71 (13.8)	
Degenerative disc disease		38 (9.6)	73 (14.2)	
Spinal stenosis		181 (45.7)	179 (34.8)	
Spondylolisthesis		92 (23.2)	127 (24.7)	**0.003**
Deformity		12 (3.0)	32 (6.2)	
Tumor		9 (2.3)	6 (1.2)	
Others		11 (2.8)	26 (5.1)	
Chief Complaint (n, %)	910			
Back Pain		48 (12.1)	113 (22.0)	
Neck Pain		2 (0.5)	8 (1.6)	
Radiculopathy		177 (44.7)	202 (39.3)	**0.001**
Myelopathy		54 (13.6)	76 (14.8)	
Neurogenic Claudication		112 (28.3)	109 (21.2)	
Others		3 (0.8)	6 (1.2)	
Body mass index in kg/m^2 (mean ± SD)	910	29.2 (5.4)	29.3 (5.9)	0.86
Any nicotine products (n, %)	910	62 (15.7)	112 (21.8)	**0.02**
High school or less (n, %)	877	143 (37.4)	209 (42.2)	0.15
Single (n, %)	900	89 (22.7)	141 (27.8)	0.085
History of spine surgery (n, %)	910	81 (20.5)	148 (28.8)	**0.004**
ASA physical status (n, %)	910			
ASA 1		74 (18.7)	106 (20.6)	
ASA 2		253 (63.9)	292 (56.8)	0.14
ASA 3		67 (16.9)	114 (22.2)	
ASA 4		2 (0.5)	2 (0.4)	
Sleep difficulty (n, %)	892	267 (69.7)	418 (82.1)	**<0.001**
Daily non-opioid medication (n, %)	885	159 (41.4)	260 (51.9)	**0.002**
Daily opioid medication (n, %)	861	69 (18.4)	208 (42.9)	**<0.001**
Daily antidepressant medication (n, %)	841	66 (17.7)	143 (30.6)	**<0.001**
Daily neuroleptic medication (n, %)	854	111 (29.4)	184 (38.7)	**0.005**
Chronic pain	865	265 (71.2)	423 (79.5)	**<0.001**
Preoperative neck or back pain measured by NRS (mean ± SD)	896	6.0 (2.7)	7.1 (2.2)	**<0.001**
Depression on patient health questionnaire-9 (mean ± SD)	849	8.0 (5.7)	10.7 (6.4)	**<0.001**

Severe preoperative disability on NDI or ODI* (n, %)	852	179 (37.1)	304 (56.7)	**<0.001**
Surgical approach (n, %)	910			
Any anterior		85 (21.5)	117 (22.8)	0.52
Any posterior		297 (75.0)	372 (72.4)	
Any anterior and posterior		14 (3.5)	25 (4.9)	
≥3 motion segments operation (n, %)	910	58 (14.7)	130 (25.3)	**<0.001**
Fusion surgery (n, %)	910	189 (47.7)	357 (69.5)	**<0.001**
Minimally invasive surgery (n, %)	910	90 (22.7)	132 (25.7)	0.30
Revision surgery (n, %)	910	47 (11.9)	84 (16.3)	0.057
Grade 3 osteotomy or more† (n, %)	910	14 (3.5)	21 (4.1)	0.67

*Neck Disability Index ≥50 and Oswestry Disability Index >40

†At least pedicle or partial body resection

NRS- numeric rating scale, CI- confidence interval, ASA- American Society of Anesthesiologists, SD- standard deviation

Table 3. Clinical score assigned to each predictor for poor acute postoperative pain control after elective spine surgery (numeric rating scale for pain at rest >4).

Predictor	Adjusted OR (95%CI)	p-value	Score
Age <70 years	1.69 (1.20-2.37)	0.002	2
Female Sex	1.73 (1.29-2.30)	<0.001	2
Daily preoperative opioid use	2.72 (1.93-3.85)	<0.001	3
Preoperative NRS neck/back pain>7	1.45 (1.07-1.98)	0.018	1
Moderate to Severe depression (PHQ-9≥10)	1.39 (1.02-1.91)	0.038	1
≥3 motion segments operation	2.01 (1.38-2.93)	<0.001	2
Fusion Surgery	2.12 (1.57-2.88)	<0.001	2
Total Score			**0 to 13**

PHQ-9- patient health questionnaire-9

Table 4. Calgary Postoperative Pain after Spine Surgery (CAPPS) Score. Stratum specific likelihood ratios and predicted probability for poor postoperative pain control for each tier of the CAPPS score.

Eight-Tier CAPPS Score	Stratum Specific LR (95% CI)	Predicted Probability of Poor Pain Control (NRS>4) (%)
0-2	0.25 (0.16-0.37)	24.2
3	0.46 (0.26-0.81)	37.6
4	0.46 (0.33-0.64)	37.3
5	1.23 (0.79-1.91)	61.5
6	1.08 (0.76-1.53)	58.4
7	1.44 (0.99-2.09)	65.1
8	1.77 (1.09-2.89)	69.7
9-13	4.40 (2.90-6.67)	85.1
Three-Tier CAPPS Score		
Low-risk (0 to 4)	0.36 (0.30-0.45)	32.0
High-risk (5 to 8)	1.32 (1.12-1.55)	63.0
Extreme-risk (9 to 13)	4.40 (2.90-6.67)	85.1

Pretest probability of outcome used for calculation- 56.5%
LR- likelihood ratio; NRS- numeric rating scale

Figure

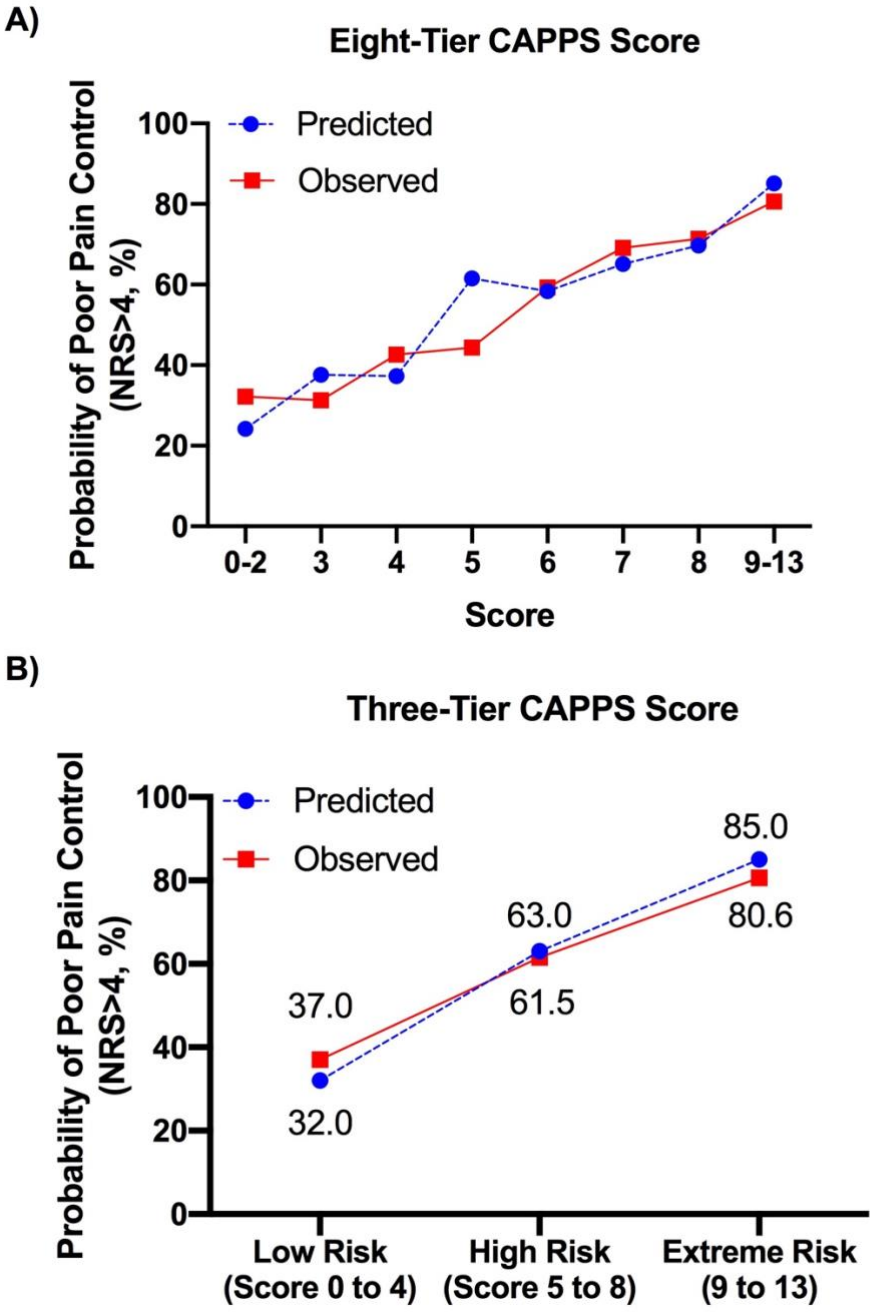


Figure 1. Calibration for the Calgary Postoperative Pain after Spine Surgery (CAPPS) score. Predicted vs. observed probability of developing poor pain control (numeric rating scale for pain>4) after elective spine surgery in the validation cohort (n=310). A) Probabilities across the eight-tier CAPPS scores and B) three-tier CAPPS scores.

Supplementary Tables

eTable S1. Variable definitions.

Variables	**Type of Variable**	**Definition**
Age in years	Continuous	Age at time of surgery in years
Female sex	Categorical	Female sex
Principal pathology • Disc herniation • Degenerative disc disease • Stenosis • Spondylolisthesis • Deformity • Tumor • Others	Categorical	Principal radiographic pathology on MRI or CT • Disc herniation must accompany radiculopathy symptoms • Stenosis must not accompany spondylolisthesis
Chief Complaint • Back pain • Neck pain • Radiculopathy • Myelopathy • Neurogenic claudication • Others	Categorical	Chief complaint from the patient
Body Mass Index	Continuous	Kg/m^2

Any nicotine products	Categorical	Cigarette smoking, smokeless tobacco, or any nicotine containing products
High school education or less	Categorical	Less than or equal to high school education
Single	Categorical	Single, divorced or widowed
History of spine surgery	Categorical	Any history of previous spine surgery
American Society of Anesthesiologist (ASA) physical status • ASA 1 • ASA 2 • ASA 3 • ASA 4	Categorical	Classification of patient's physiological status. • ASA 1: Normal healthy patient • ASA 2: Patient with mild systemic disease • ASA 3: Patient with severe systemic disease that is non-life threatening • ASA 4: Patient with severe systemic disease that is a constant threat to life
Sleep difficulty	Categorical	Sleep is disturbed >1 hour or use of pain medication required for sleep
Daily non-opioid medication	Categorical	Daily use of any over the counter (acetaminophen, ibuprofen, naproxen, and asprin), prescription non-steroidal anti-inflammatory (diclofenac and

		celecoxib), and muscle relaxants (cyclobenzaprine, acetaminophen/methocarbamol, methocarbamol).
Daily opioid medication	Categorical	Daily use of any opioid medications (e.g., morphine, oxycodone, hydromorphone, tramadol, and codeine) including long-acting formulations.
Daily antidepressant medication	Categorical	Daily use of any antidepressant medications (e.g., citalopram, escitalopram, duloxetine, paroxetine, fluoxetine, bupropion, sertraline, and amitriptyline).
Daily neuroleptic medications	Categorical	Daily use of any neuroleptic medications (e.g., pregabalin, gabapentin, clonazepam, carbamazepine).
Chronic pain	Categorical	Taking medication for back/neck pain for >3 months
Preoperative neck or back pain measured by NRS	Continuous	Preoperative NRS neck and/or neck pain at time of pre-treatment questionnaire.
Depression on patient health questionnaire-9	Continuous	Validated questionnaire for depression.

Severe preoperative disability measured by Oswestry Disability Index or Neck Disability Index	Categorical	Oswestry Disability Index >40 or Neck Disability Index ≥ 50.
Surgical approach • Any anterior • Any posterior • Any front-back	Categorical	Surgical approach for the spine procedure.
≥3 motion segments operation	Categorical	Surgery involves 3 or more motion segments of the spine
Fusion surgery	Categorical	Fusion surgery was performed
Minimally invasive surgery (MIS)	Categorical	Any surgery that used tubular techniques, direct lumbar interbody fusion, oblique lateral interbody fusion, and percutaneous screws. Anterior lumbar interbody fusion and anterior lumbar disc arthroplasty was not considered MIS.
Revision surgery	Categorical	Any surgery that utilized the same surgical approach as the previous surgery (e.g., L4/5 anterior lumbar interbody fusion was not considered a revision surgery if the patient previously had a L4/5 posterior laminectomy).

Grade 3 osteotomy or more		At least pedicle/partial vertebral body resection (partial wedge resection of a segment of posterior vertebral elements with pedicles), as defined by Schwab et al (2014)[131].

1. Schwab F, Blondel B, Chay E, et al. The comprehensive anatomical spinal osteotomy classification. *Neurosurgery.* 2014;74(1):112-120; discussion 120.

MRI- magnetic resonance imaging, CT- computed tomography, NRS- numeric rating scale

eTable S2. List of variables used for multiple imputation in the model development cohort (n=910).*

List of variables included in the multiple imputation procedure	Number of missing data (n, %)
Poor pain control (primary outcome)	0 (0)
Location of surgery (cervical vs. thoracolumbar)	0 (0)
Age	0 (0)
Any nicotine product	0 (0)
History of spine surgery	0 (0)
Fusion surgery	0 (0)
≥3 motion segments operation	0 (0)
Revision surgery	0 (0)
Preoperative NRS neck or back pain	14 (1.5)
Depression on patient health questionnaire-9	61 (6.7)
Single	10 (1.1)
Sleep difficulty	18 (2.0)
Daily non-opioid medication	25 (2.7)
Daily opioid medication	49 (5.4)
Daily antidepressant medication	69 (7.6)
Daily neuroleptic medications	56 (6.2)
Chronic Pain	45 (4.9)
Severe Oswestry Disability Index or Neck Disability Index	58 (6.4)

* The "mi impute" command was used in STATA version 15 (StataCorp, College Station, Texas).

eTable S3. Rubric for dichotomizing continuous and ordinal variables from the *Canadian Spine Outcomes and Research Network* registry.

Variables	Variables in the CSORN registry	Final dichotomized variable*	Rationale
Age in years	• Continuous in years	• >70 years • ≤70 years	No accepted threshold found in the literature. 70 years was chosen as it corresponded to the 75th percentile in our database

Any nicotine use	1. Cigarette smoking 2. Smokeless tobacco 3. Nicotine patches or other products 4. No, quit within last 3 months 5. No 6. Choose not to answer	• Any nicotine product use • No nicotine product use	We wanted to compare patients who were consuming nicotine vs none
High school education or less	1. Less than high school 2. High school diploma 3. Technical school or associate degree 4. College/university/undergraduate degree 5. Choose not to answer	• Less than or equal to high school • More than high school	We wanted to compare the effects of less than or equal to high school vs. more than high school
Single	1. Single 2. Married, engaged, or common-law 3. Divorced/separated 4. Widowed 5. Choose not to answer	• Single, divorced, or widowed. • Married, engaged or common law	We wanted to compare the impact of patients in a relationship vs. not
Sleep difficulty	The sleep difficulty was a composite of the "sleep" question in the Oswestry Disability Index and Neck Disability Index. <u>Oswestry Disability Index for Sleep</u> 1. I have no trouble sleeping 2. My sleep is slightly disturbed for less than 1 hour 3. My sleep is mildly disturbed for up to 1 to 2 hours 4. My sleep is moderately disturbed for up to 2 to 3 hours 5. My sleep is greatly disturbed for up to 3 to 5 hours 6. My sleep is greatly disturbed for up to 3 to 5 hours 7. My sleep is completely disturbed up to 5 to 7 hours <u>Neck Disability Index for Sleep</u> 1. Pain does not prevent me from sleeping well 2. I can sleep well only by use of pain medication	• Sleep is disturbed for >1 hour or use of pain medication is required for sleep • Sleep is not disturbed and does not require the use of pain medications	Preoperative sleep difficulty has previously been identified as a risk factor for poor pain control after surgery.

	3. Even when I take pain medication, I sleep less than six hours 4. Even when I take pain medication, I sleep less than four hours 5. Even when I take pain medication, I sleep for less than two hours 6. Pain prevents me from sleeping well		
Daily non-opioid medication use	1. None 2. Intermittent 3. Daily	• Daily use • None or intermittent use	We wanted to compare daily non-opioid medication use vs. those who take it intermittently or never.
Daily opioid medication use	1. None 2. Intermittent 3. Daily	• Daily use • None or intermittent use	We wanted to compare daily opioid medication use vs. those who take it intermittently or never.
Daily anti-depressant use	1. None 2. Intermittent 3. Daily	• Daily use • None or intermittent use	We wanted to compare daily use vs. those who take it intermittently or never.
Daily neuroleptic use	1. None 2. Intermittent 3. Daily	• Daily use • None or intermittent use	We wanted to compare daily use vs. those who take it intermittently or never.
Chronic pain	1. Taking pain medications less than 3 months 2. Taking pain medications between 3 months to 1 year 3. Taking pain medications over 1 year	• >3 months use of pain medication • Less than 3 months use	Chronic pain is typically defined as having pain for >3 months.

		of pain medication	
Pre-operative Neck/Back Pain measured by NRS	• Ordinal (0 to 10)	• NRS>7 • NRS≤7	Severe pain is defined as NRS>7. By setting a high threshold, we also believe this predictor may capture patients who are pain catastrophizers
Depression on patient health questionnaire-9	• Continuous	• Moderate to severe depression (≥10) • None to mild depression (<10)	Patients who score moderate to severe depression are more likely to be diagnosed with clinical depression (88% sensitivity and specificity). This threshold has also been commonly used in previous pain studies
Severe disability on ODI or NDI	This predictor was developed by combining the definition of severe disability on Oswestry Disability Index (ODI) for thoracolumbar surgery patients and Neck Disability Index (NDI) for cervical surgery patients.	• ODI >40 or NDI ≥50 • ODI ≤40 or NDI <50	We wanted to compare patients who were severely disabled by their condition compared to those who were mildly to moderately disabled.
≥3 motion segments operation	• Ordinal	• ≥3 motion segments operation	During exploratory data analysis

		• <2 motion segment operation	it was found ≥3 motion segments operation yielded the largest proportion of patients with poor pain control compared to other levels.
Grade 3 osteotomy or more	• Grade 1 • Grade 2 • Grade 3 • Grade 4 • Grade 5 • Grade 6	• Grade 3 osteotomy or more • Less than grade 3 osteotomy	Grade 3 osteotomy at least involves partial resection of the vertebral body which considered as a more "complex" procedure

*The first listed item was coded as "1" the second as "0" during analyses
"Choose not to answer" were categorized as missing data.

eTable S4. Patient characteristics in the model development and validation cohorts.

Characteristic	Model Development Cohort	Validation Cohort
Age in Years (mean ± SD)	59.8 (13.8)	58.8 (13.0)
Female sex (n, %)	442 (48.6)	188 (48.2)
Principal pathology (n, %)		
Disc Herniation	124 (13.6)	48 (12.3)
Degenerative disc Disease	111 (12.2)	55 (14.1)
Stenosis	360 (39.6)	149 (38.2)
Spondylolisthesis	219 (24.1)	87 (22.3)
Deformity	44 (4.8)	27 (6.9)
Fracture-traumatic	1 (0.1)	1 (0.3)
Fracture-pathological	1 (0.1)	1 (0.3)
Tumor	15 (1.7)	8 (2.1)
inflammatory	1 (0.1)	1 (0.3)
infection	1 (0.1)	0 (0)
Others	33 (3.6)	13 (3.3)
Chief Complaint (n, %)		
Back Pain	161 (17.7)	75 (19.2)
Neck Pain	10 (1.1)	7 (1.8)
Radiculopathy	379 (41.7)	169 (43.3)
Myelopathy	130 (14.3)	50 (12.8)
Neurogenic claudication	221 (24.3)	83 (21.3)
Deformity	4 (0.4)	1 (0.3)
Others	5 (0.6)	5 (1.3)
Poor Postoperative Pain Control, NRS>4 (n, %)	514 (56.5)	224 (57.4)
BMI (mean ± SD)	29.4 (5.7)	29.1 (5.5)
Any nicotine products (n, %)	174 (19.1)	81 (20.8)
High school or less (n, %)	352 (40.1)	151 (39.8)
Single (n, %)	230 (25.6)	110 (28.3)
History of spine surgery (n, %)	229 (25.2)	101 (25.9)
ASA (n, %)		
ASA 1	180 (19.8)	76 (19.5)
ASA 2	545 (59.9)	232 (59.5)
ASA 3	181 (19.9)	82 (21.0)
ASA 4	4 (0.4)	0 (0)
Sleep difficulty (n, %)	685 (76.8)	300 (78.3)
Medications (n, %)		
Non-opioid	419 (47.3)	193 (51.2)
Opioid	277 (32.2)	119 (33.0)
Antidepressant	209 (24.9)	82 (23.2)
Neuroleptic	295 (23.5)	122 (34.6)
Chronic Pain (n, %)	688 (79.5)	293 (79.2)

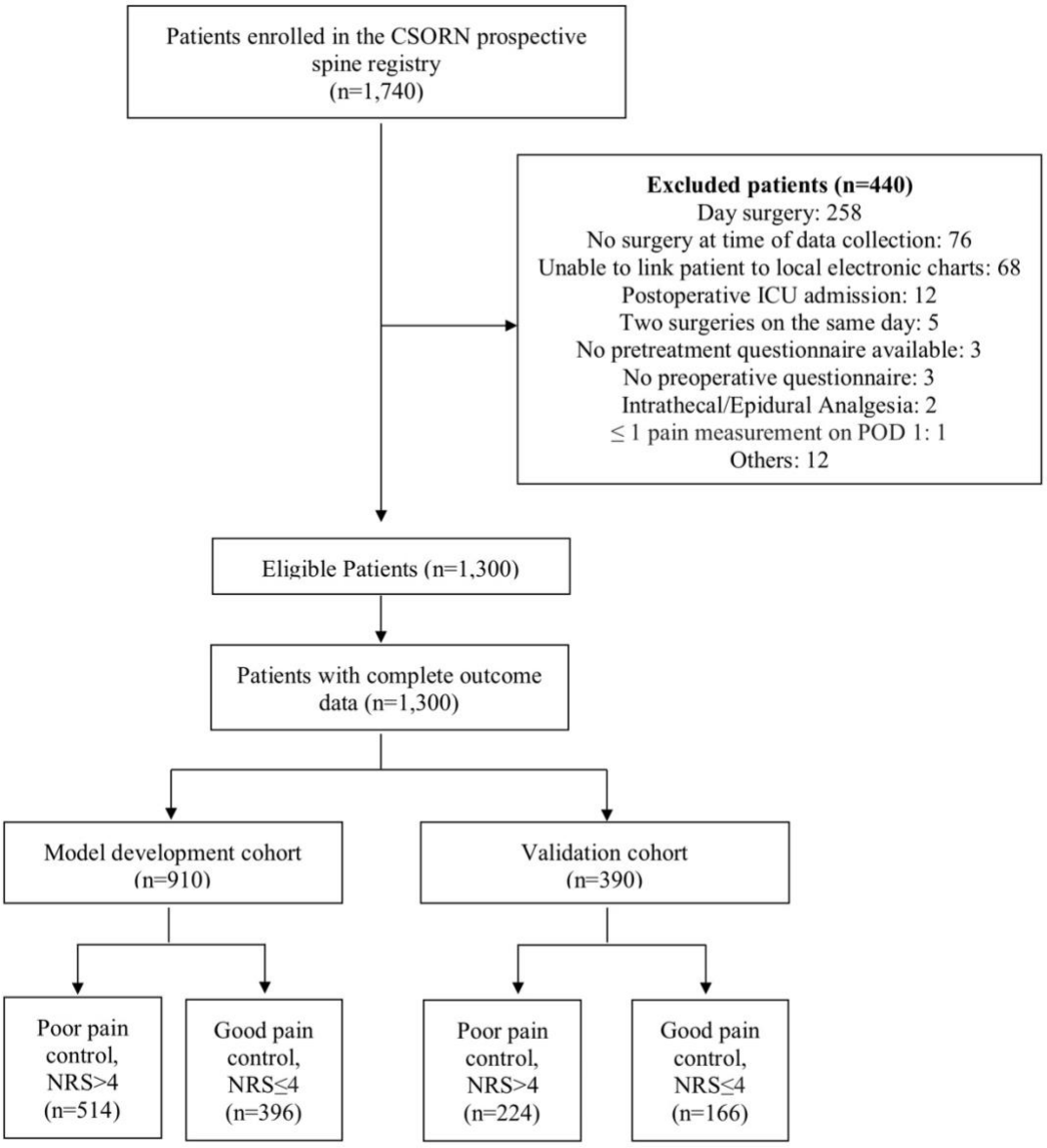
Preoperative NRS neck or back pain (mean ± SD)	6.6 (2.5)	6.8 (2.3)
Depression on patient health questionnaire-9 (mean ± SD)	9.5 (6.2)	9.8 (6.3)
Preoperative severe disability on NDI or ODI (n, %)	483 (56.5)	208 (56.2)
Surgical Approach (n, %)		
Any Anterior	202 (22.2)	109 (28.0)
Any Posterior	669 (73.5)	261 (66.9)
Any Anterior and Posterior	39 (4.3)	30 (5.1)
Levels (mean ± SD)	1.9 (1.6)	1.9 (1.3)
Fusion surgery (n, %)	546 (60.0)	247 (63.3)
Minimally invasive surgery (n, %)	222 (24.4)	96 (24.6)
Revision surgery (n, %)	131 (14.4)	58 (14.9)
Grade 3 osteotomy or more (n, %)	35 (3.9)	20 (5.1)

eTable S5. Regression coefficients with standard error for final multivariable model

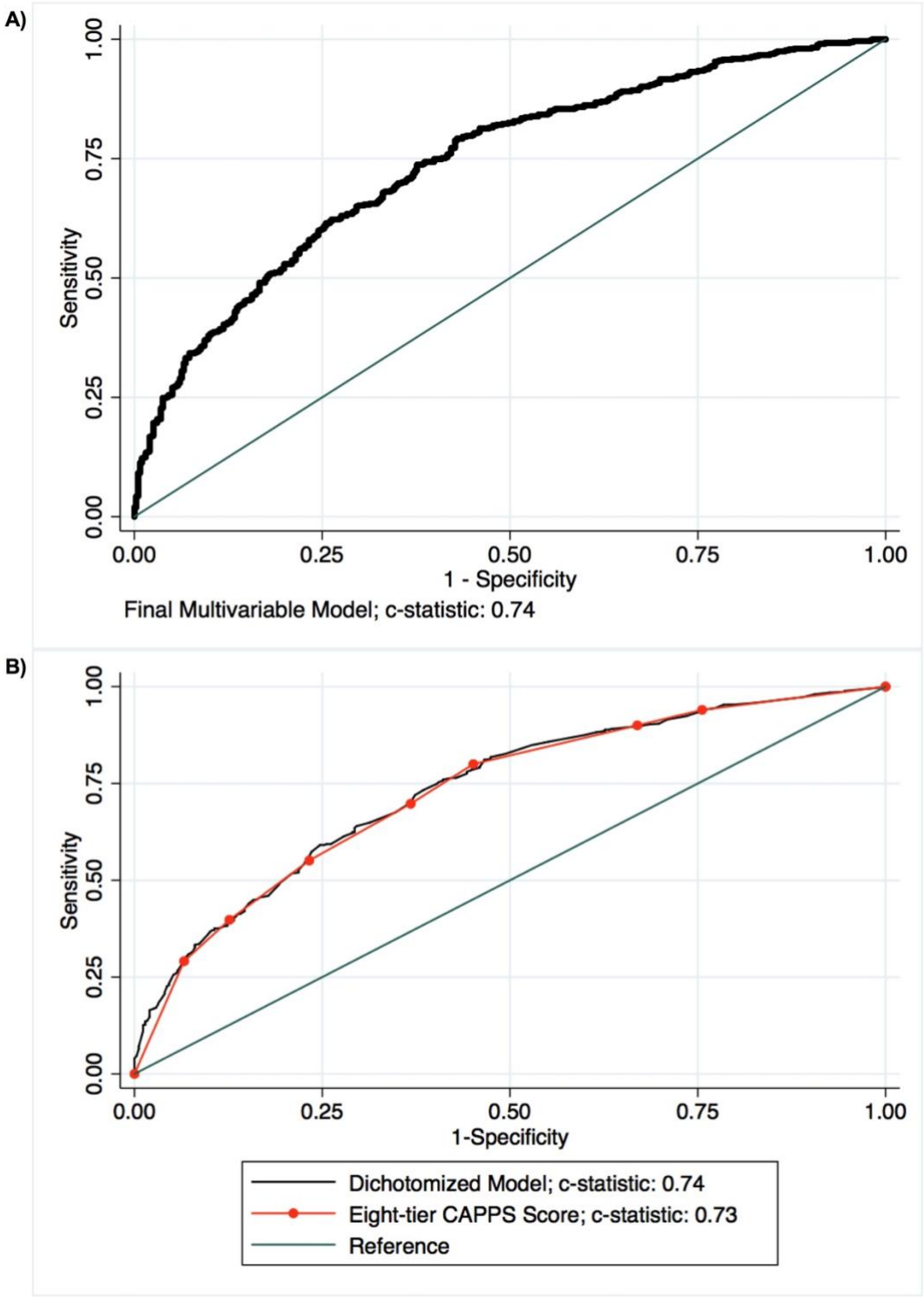
Predictor	**Regression coefficient (95%CI)**	**Standard error**	**p-value**
Age in years	-0.02 (-0.03 to 0.007)	0.006	0.001
Female sex	0.49 (0.20 to 0.79)	0.15	0.001
Daily opioid medication	0.96 (0.61 to 1.30)	0.18	<0.001
Preoperative NRS neck or back pain	0.12 (0.05 to 0.19)	0.03	<0.001
Depression on patient health questionnaire-9	0.03 (0.001 to 0.06)	0.01	0.039
≥3 motion segments operation	0.77 (0.38 to 1.16)	0.20	<0.001
Fusion surgery	0.75 (0.45 to 1.06)	0.16	<0.001
Location of surgery	-0.048 (-0.41 to 0.31)	0.18	0.80
Intercept	-0.77 (-1.60 to 0.05)	0.42	0.07

Coding of predictors: Age, continuous; female sex, 1-female/0-male; daily opioid medication, 1-yes/0-no, preoperative NRS neck/back pain, continuous; patient health questionnaire-9, continuous; >2 motion segments, 1-yes/0-no, fusion surgery, 1-yes/0-no; location of surgery, 1-thoracolumbar/0-cervical. CI-confidence interval.

Supplementary Figures



eFigure S1. Participant flow diagram. CSORN: Canadian Spine Outcomes and Research Network; NRS: numeric rating scale; POD: postoperative day



eFigure S2. Receiver Operating Characteristic (ROC) Curves. A) The final multivariable model. B) Dichotomized multivariable model (black) and eight-tier Calgary Postoperative Pain after Spine Surgery (CAPPS) score (orange).

CHAPTER 4: CONCLUSION

Summary of Findings

Chapter 2:

This systematic review and meta-analysis reinforce the notion that postoperative pain is treated sub-optimally across surgical disciplines. The incidence of poor pain control across disciplines ranged between 14.0% to 78.4%.[153] In this study, nine significant preoperative predictor of poor postoperative pain control was found: younger age, female sex, smoking history, history of depressive symptoms, history of anxiety symptoms, sleep difficulty, higher BMI, presence of preoperative pain, and history of preoperative analgesia use.[153] The strongest negative predictors of poor pain control were history of sleeping difficulty and history of depression.[153]

Chapter 3

In this retrospective cohort study, a comprehensive understanding of the predictors of poor postoperative pain control after elective spine surgery was determined. The incidence of poorly controlled pain in this study was 57%. Seven significant predictors were associated with poor pain control: younger age, female sex, preoperative daily opioid medication use, higher preoperative neck or back pain intensity, higher PHQ-9 depression score, ≥3 motion segment operation, and fusion surgery. These predictors were used to develop a three-tier CAPPS score. Patients classified to low-, high-, and extreme-risk groups by the CAPPS score had 32%, 63%, and 85% predicted probability of developing poorly controlled pain, respectively. This closely mirrored the observed probability of 37%, 62%, and 81% in the same risk-groups for poor pain control in the validation cohort.

Strengths & Limitations

Chapter 2:

The strengths of the systematic review are numerous, including the rigorousness of how the search strategy was developed. The search strategy was developed using the PRESS method with the assistance of two health research librarians from the University of Calgary.[103] The goal of PRESS is to increase the comprehensiveness and improve the coverage of the search strategy to minimize the chance that important studies are missed.[103] In this process, a search strategy is submitted for peer review by the researcher. This review includes an appraisal of whether the search strategy matches the research question, Boolean and proximity operators, subject headings, text word searching (free text), spelling syntax and line numbers, and limits and filters.[103] If major revisions are requested after the peer review process, a second PRESS peer review of the revised search strategy is conducted. This iterative process is continued until both the researcher and the peer reviewer are satisfied with the final search strategy.[103] Another strength of this paper is the thorough review and meta-analysis of numerous preoperative predictors for poor acute postoperative pain after surgery, making the results of the study generalizable to numerous surgical disciplines. In addition, the included studies represented publications from diverse geographic locations, which further increases the generalizability of the findings.

There are also several limitations to this study. As discussed in the introductory chapter, for a meta-analysis to be readily interpretable, the included studies should be similar in terms of

patient population, timing and definitions of the outcome measure, and the interventions received. There were clear differences in the surgical disciplines included, the timing of postoperative pain measurement, and definition of inadequate pain control in the included studies. Given these differences, it is more difficult to interpret the meaning of the specific measure of association for each predictor. For example, younger age was found to be a significant predictor for poor pain control, with an OR of 1.18.[153] However, the definition of "younger age" varied between ≤31 to <70 years between studies in part reflecting the heterogeneity of the surgical procedures included (e.g., caesarean section [younger patients] vs. total knee replacement [older patients]). This makes the quantitative interpretation of the OR difficult. Another limitation is the effect of confounding and bias when performing meta-analyses of observational studies.[45] In this review, 36% of the studies did not have adequate adjustment for confounders (operationalized as adjusting for ≥3 potential confounders). High-quality observational studies attempt to adjust for as many potential confounders of the disease-exposure relationship as possible. However, depending on the sample size of the study, and the limitation of the primary database, adjustment for potential confounders may be inadequate or unequal between studies. As a result, pooled estimates from observational studies may yield associations that may deviate from the true underlying disease-exposure relationship beyond what is expected from random error. Further, residual confounding (e.g., confounders that were not measured, imprecise measurement of the confounder) is always a concern in observational studies. Further, a fallacy of meta-analysis of observational studies is that studies with larger sample size are of higher quality, and hence more statistical weight should be given to these studies when pooling results.[45] When examining randomized controlled trials, giving more statistical weight to larger studies is appropriate because their main limitation is usually the lack

of precision in the effect estimates. In a meta-analysis of observational studies, the main problem is not precision, but biased or confounded studies. It is more important to give higher statistical weight to smaller studies that are well-designed than to larger studies that are poorly conducted. However, the DerSimonian and Laird random-effects model used in this study assign more weight to studies that have more precise effect estimates (e.g., larger sample size) compared to those studies that have less.

Chapter 3

The strengths of this study include the prospective nature in which candidate variables were collected as part of the CSORN registry protocol. Further, the selection of candidate variables was performed rigorously, being informed by a systematic review and meta-analysis and expert consensus using pre-specified criteria for selection. Prediction models must balance the number of candidate variables included with the degree of unique prognostic value they provide. Often models are developed based on a larger number of candidate variables than are required,[128] which may lead to issues of multiple testing and finding spurious associations with the outcome. However, if too few prognostically valuable variables are included, the model's performance and clinical usefulness suffers. This study mitigated these potential pitfalls by using a systematic review and expert consensus to ensure prognostically important variables are not missed while eliminating variables that were judged to be not important in predicting the outcome. The model development cohort had sufficient sample size to adequately investigate 25 degrees of freedom in a multivariable model to avoid biased regression coefficients and inflated standard error estimates. Selection bias secondary to patient attrition can be a significant source of bias in observational cohort studies due to the extended follow-up that is usually required between

exposure measurement and outcome collection.[113] Fortunately, in this study there was no patient attrition. Since the outcome data (e.g., NRS for pain in the first 24-hours after surgery) was collected retrospectively in this study, an effort was made to collect a subset of this data in duplicate. The percentage major error rate in abstracting the outcome data was 1.0%. This low error rate gives confidence that the outcome data collection procedure was performed carefully and meticulously. Finally, of the seven predictors found to be significant in predicting poor postoperative pain control after elective spine surgery, five of those predictors were the same predictors found to be predictive of poor pain control across surgical disciplines in the systematic review and meta-analysis: younger age, female sex, preoperative pain, preoperative analgesic use, and depression. The comparability of the results between the two studies provides more confidence that these risk factors are indeed important in predicting poor pain control. The two other predictors: spine fusion and number of motion segment surgery pertain to risk factors that are specific to the spinal surgery population.

There are also limitations to this study. Missing data were present for candidate variables in this study. If missing data for candidate variables are related to the outcome of the study in a way that differs depending on the various exposures, selection bias will occur.[113] This selection bias can either overestimate or underestimate the measure of association. The effect of missing data was mitigated by using a multiple imputation procedure. However, for multiple imputations to be valid, the "missingness" of the data should be 'missing completely at random' or 'missing at random'. If data are missing not at random, then traditional multiple imputation techniques can lead to severely biased parameter estimates. Unfortunately, it is often challenging to ascertain the degree of 'missing not at random' in a dataset. One method to demonstrate the robustness of a

model after multiple imputation is to perform a sensitivity analysis where the multivariable model using complete case analysis is compared with the model using multiple imputation. When complete case analysis was repeated in the model development cohort, 789/910 patients were included in the multivariable analysis. This model yielded the same seven significant predictors for poor postoperative pain control after elective spine surgery with a c-statistics of 0.75. The similar results obtained using two different methods of dealing with missing data suggest our final model is robust.

As discussed in chapter 3, there could be other prognostically important variables (e.g., preoperative anxiety) that were not included in the multivariable model. Future studies should attempt to update this prediction score in order to improve its predictive performance. However, the most useful prediction tools are often ones that have a small number of predictors while having maximal performance. There was close concordance between the predicted vs. observed probability of poor postoperative pain control in the three-tier CAPPS score. However, the percentage misclassification between low- and high- or extreme-risk groups of 38.0% and 29.9%, respectively. This means, approximately 30% of patients were misclassified as having good pain control when, in fact, they had poor pain control, and vice versa. This highlights the difficulty in developing a prediction rule to predict pain, which can be affected by a multitude of psychosocial, biological, and environmental factors. Further, the relatively low sensitivity (60%) to detect poor pain control between the low- vs. extreme-risk group suggests the score can be missing up to 40% of patients that will develop poor pain control in this group. Fortunately, patients who are misclassified based on the CAPPS score will still receive routine postoperative pain management, and there would be no additional risk to the patient. However, this

misclassification can lead to overuse or underuse of preventative preoperative and perioperative treatment strategies and subjecting patients to unnecessary risk from these treatments. Lastly, before widespread adoption of the CAPPS score, the adequate predictive performance of this score should be demonstrated in a separate external population.

Concluding Remarks

Access to optimal pain management following surgery is a fundamental human right. However, the incidence of poor pain control following spine surgery continues to be high.[137] The incidence of poor postoperative pain control in our study cohort was 56.7% after elective spine surgery. This high incidence of poorly controlled pain can be partly explained by the lack of understanding of the patient and surgical risk factors for poor pain control and the availability of a prediction tool to allow identification of at-risk patients before surgery. As such, the overall goals of this thesis were to determine the predictors for poor postoperative pain control following elective spine surgery and to develop a simple to use clinical prediction score (the CAPPS score) that allows clinicians to risk-stratify patients in the preoperative setting so that anticipatory and personalized clinical care pathways can be developed to improve postoperative pain outcomes.

To my knowledge, Chapter 3 represents the first and largest series in the literature evaluating postoperative pain following spine surgery. We found seven significant predictors of poor postoperative pain control, and they were incorporated into a clinical prediction score. This final prediction score and its risk-stratified derivation were rigorously tested and internally validated.

We found preoperative daily opioid use, depression, and preoperative axial neck or back pain to be modifiable risk factors for the development of poorly controlled pain following spine surgery. The identification of these modifiable risk factors will allow clinicians to develop anticipatory preoperative and perioperative treatment strategies to mitigate the chance patients will develop poor pain control following surgery. Equipped with this knowledge and the ability to identify high-risk patients in the preoperative setting, we can now take a preventative approach instead of a reactive approach to the management of postoperative pain. This paradigm shift in management should lead to improvements in postoperative pain intensity, patient satisfaction, length of hospital stay, reduction in postoperative opioid use, and other pain-related complications such as the development of persistent post-surgical pain. Future studies, as outlined in the next section, will aim to implement these preventative approaches and to study the effects on postoperative pain and surgical outcomes.

Future Directions & Knowledge Translation

External Validation of Clinical Prediction Score

The clinical prediction score developed during this thesis was internally validated using a split-sample technique. Hence, before widespread adoption of the prediction score, it must be externally validated. We plan to temporally- and spatially-externally validate our prediction model in Calgary and at a geographically distinct spine center.

Preoperative Opioid Tapering and Acceptance and Commitment Therapy

The results from this thesis has highlighted the importance of preoperative opioid deprescribing and modifying psychosocial risk factor such as depression to improve postoperative pain outcomes. The long wait-times for spinal surgery in Canada provides a distinct opportunity to optimize patients on these risk factors before surgery. We plan to test a preoperative opioid tapering program and a psychotherapy program aimed at improving preoperative depression scores. We hope this study will lead to improved postoperative pain control and surgical outcome (e.g., ODI, NDI) after spine surgery.

Development of a Perioperative Personalized Clinical Care Pathway

The optimization of preoperative risk factors using a preoperative opioid tapering program or a psychotherapy program is time consuming and resource intensive. Further, the skills required to implement these strategies are often beyond the expertise of a spine surgeon or other specialists involved in the perioperative care of a surgical patient. As such, there is a need to develop a perioperative treatment strategy that is personalized to a patient's specific risk for developing poorly controlled pain following spine surgery. We plan to develop a personalized clinical care pathway for each of the three risk-groups found in this thesis. We will then evaluate the impact of these strategies as it relates to various surgical outcomes.

Knowledge Translation

The increased emphasis on practicing evidence-based precision medicine has led to a proliferation of clinical prediction scores.[29] To ensure the findings from this thesis benefit patients, it is important to have a knowledge translation plan. The CAPPS score would be of interest to health care professionals that are involved in any part of a patient's surgical journey;

from the initial preoperative consultation until their transition back to their primary care team. The key stakeholders involved in this patient pathway includes anesthesiologists, perioperative acute pain specialists, spine surgeons, family physicians, residents and nurses.

The primary goals of the knowledge translation plan would be to increase knowledge/awareness and improve the utilization of the CAPPS score. To facilitate knowledge dissemination, the results from this thesis would be presented at national and international spine meetings. The results would also be disseminated by publishing the results in a reputable surgery or spine surgery journal. Locally, we would share the results with the Calgary Spine Program and devise an effective strategy to incorporate the CAPPS score into preoperative spine clinics so appropriate patient education can be performed on expected pain control following spine surgery. We can monitor and document the utilization rates of the CAPPS score during preoperative consultation and measure the impact of education on postoperative pain control. We would consider an absolute increase of 10% in the use of the CAPPS score as the definition for success.[62] This would be followed by education sessions with residents who are usually the frontline physicians who manage postoperative pain after spine surgery. To ensure sustainability, the results from the knowledge translation initiative would be fed back to important stakeholders.

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Dear Dr. Steven Casha,

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Dear Jonathan Cunningham,

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Dr. Nathalie Jette Date (mm/dd/yy)

April 1st, 2019

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Dear Dr. Jay Riva-Cambrin,

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You are receiving this letter because you are a co-author for one of two manuscripts that is part of Dr. Michael M.H. Yang's Master of Science (MSc) thesis.

As a MSc degree requirement, the Department of Community Health Science and the Faculty of Graduate Studies requires all theses to be deposited to the institutional repository at the University of Calgary and the Library and Archives Canada. Information regarding the University of Calgary Theses Repository- "the vault" can be found at http://theses.ucalgary.ca/Library and the Archives Canada can be found at http://collectionscanada.gc.ca/obj/s4/f2/frm-nl59-2-e.pdf

I am seeking for your permission to include the following paper/manuscript to the repositories listed above:

1) A Clinical Prediction Model for Poor Postoperative Pain Control After Elective Spine Surgery

If agreeable, please sign and date below:

_____ _____

Dr. Tolulope Sajobi Date (mm/dd/yy)