

BMJ Open Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis

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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 PsycINFO 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 to 1.32], number of studies, n=14), female sex (OR 1.29 [95% CI 1.17 to 1.43], n=20), smoking (OR 1.33 [95% CI 1.09 to 1.61], n=9), history of depressive symptoms (OR 1.71 [95% CI 1.32 to 2.22], n=8), history of anxiety symptoms (OR 1.22 [95% CI 1.09 to 1.36], n=10), sleep difficulties (OR 2.32 [95% CI 1.46 to 3.69], n=2), higher body mass index (OR 1.02 [95% CI 1.01 to 1.03], n=2), presence of preoperative pain (OR 1.21 [95% CI 1.10 to 1.32], n=13) and use of preoperative analgesia (OR 1.54 [95% CI 1.18 to 2.03], n=6). Pain catastrophising, American Society of Anesthesiologists status, chronic pain, marital status, socioeconomic status, education, surgical history, preoperative pressure pain tolerance and orthopaedic surgery (vs abdominal surgery) were not associated with 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 recognised as potentially important factors when developing discipline-specific clinical care pathways to improve pain outcomes and to guide future surgical pain research.

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INTRODUCTION

Since 1999, when the Joint Commission on Accreditation of Healthcare Organizations

Strengths and limitations of this study

- This systematic review provides a comprehensive meta-analysis on a large number of preoperative patient prognostic factors for poor acute postoperative pain control.
- The inclusion of multiple surgical specialties and articles representing diverse geographical locations increases the generalisability of the findings.
- There were a variety of definitions for poor postoperative pain control, timing of pain assessment and thresholds used to categorise continuous preoperative variables making the clinical and statistical interpretation of the meta-analysis more challenging.
- For certain preoperative variables, the number of studies included were few and may be underpowered to detect significant differences.

set the standard for the appropriate assessment and management of pain, pain has been recognised as the fifth vital sign.¹ With the ageing and growing population, the number of surgeries has increased to an excess of 280 million procedures performed globally every year.^{2–8} Numerous studies suggest poor acute postoperative pain control is common and often inadequately treated.^{9–12} Importantly, ineffective postoperative pain control is associated with poor outcomes including increased length-of-stay, sleep disturbance, prolonged time to first mobilisation and increased opioid use.^{11 13 14} Further, poor postoperative pain control is associated with delirium in the elderly, development of chronic pain syndromes, cardiopulmonary and thromboembolic complications.^{10 11 15–17} Postoperative pain may be improved by understanding the preoperative predictors of poor pain control by allowing the use of anticipatory and individualised treatments.^{18 19}

A previous systematic review reported a limited number of predictors of poor postoperative pain control including age, anxiety, preoperative pain and surgery type.²⁰ 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 was nearly a decade ago, many additional studies have been published with improved methodological rigour;^{21–24} 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 hospitalisation. This meta-analysis is important to help to identify predictors that could inform future surgical pain research and aid in the development of discipline-specific clinical care pathways (eg, enhanced recovery after surgery programmes) to improve pain outcomes.

METHODS

This review was reported according to the Meta-analyses Of Observational Studies in Epidemiology 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 (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080682).^{25–27}

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*²⁸ in consultation with two research librarians. We focused on the keywords ‘pain’, ‘pain measurement’, ‘surgery’ and ‘predictors’. We searched MEDLINE (1950 to 13 October 2017), Embase (1980 to 13 October 2017), CINAHL (1937 to 13 October 2017) and PsycINFO (1967 to 13 October 2017) (online supplementary appendix S1, online supplemental information). To maximise sensitivity for studies of prognosis, search filters were not used, and no restrictions were placed on date or language of publication.^{29 30} 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 (eg, excluded ambulatory surgery/procedures, dental procedures, carpal tunnel release, and so on), 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 minimise 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 scale (VRS) for pain are highly correlated with each other, and thus, they were considered comparable in the present study.³¹ To facilitate pooling of data, we only included studies that reported a measure of association, such as an 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 (MMHY and RLH) 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 (eg, young vs old age, or moderate vs severe pain), each stratum was treated as an independent study for the pooled analysis (no patients were analysed in duplicate).^{23 32–34} 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.³⁵ The following variables were considered to be the most important quality indicators for studies of prognosis (definition of quality indicators are in online supplementary table S1, online supplemental information)³⁵: description of population, non-biased selection, adequate follow-up (eg, postoperative pain measurements were recorded for at least 80% of study participants), predictor measurement, outcome measurement and ascertainment, adjustment for confounding variables (operationalised as adjusting for at least three potential confounders), precision of reported results (eg, reporting of CIs), as well as the use of an appropriate

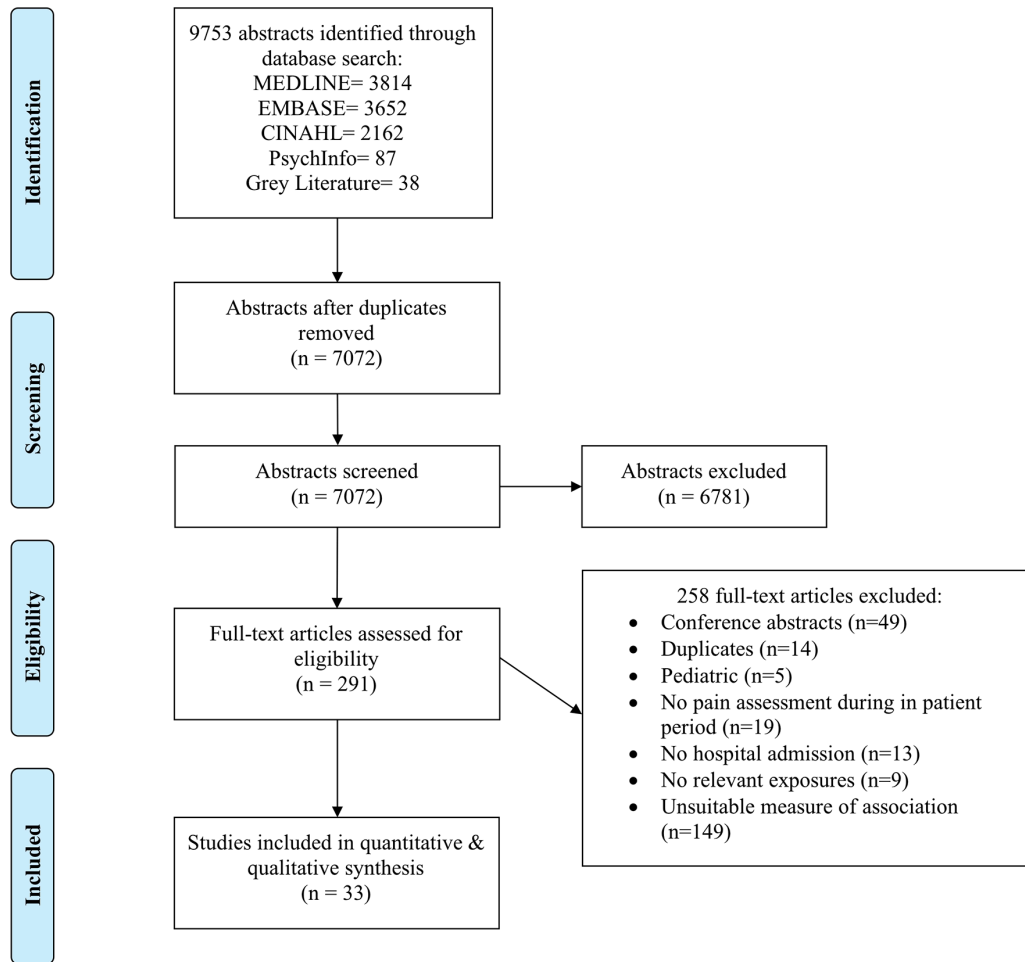


Figure 1 Systematic review and meta-analysis flow diagram. All database and grey literature search was performed on 13 October 2017.

reference standard (eg, definition of poor postoperative pain control provided).^{29 35 36} 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 2 weeks if a response was not received.

Statistical analysis

We used ORs as the common measure of association. RRs were converted to OR 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.³⁷ 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% CIs), were determined for each preoperative predictor associated with poor postoperative pain control levels using the DerSimonian and Laird random effects model and visualised 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. Level of significance was set at $\alpha = 0.05$.

Between-study heterogeneity was examined and quantified using the Cochran's Q test and I^2 statistic.³⁸ 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 (eg, operationalised 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 [eg, 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 (eg, postanesthetic 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 (eg, different surgical disciplines/procedures) or bias inherent to individual studies (eg, residual confounding and lack of blinding).³⁰

RESULTS

Literature search and study characteristics

We identified 9753 articles through the 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 ($\kappa=0.83$ [95% CI 0.71 to 0.91]). No unpublished studies were identified and included in the final analysis.

The 33 included studies represented 53362 patients with publication dates ranging between 2002 and 2017 (study characteristics of included studies are in table 1).^{19 21–24 32–34 39–63} Twenty-six studies were prospective cohort studies (79%) and seven 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 scales for pain were 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 subspecialties 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 three potential confounders, five studies (15%) did not provide definitions of preoperative

predictors and four studies (12%) did not define how their sample was selected.

Preoperative predictors of poor postoperative pain control

Of the 23 variables examined, nine statistically significant preoperative predictors of poor postoperative pain control were found: younger age (OR 1.18 [95% CI 1.05 to 1.32]), female sex (OR 1.29 [95% CI 1.17 to 1.43]), smoking (OR 1.33 [95% CI 1.09 to 1.61]), history of depressive symptoms (OR 1.71 [95% CI 1.32 to 2.22]), history of anxiety symptoms (OR 1.22 [95% CI 1.09 to 1.36]), sleep difficulties (OR 2.32 [95% CI 1.46 to 3.69]), higher body mass index (BMI) as a continuous variable (OR 1.02 [95% CI 1.01 to 1.03]), presence of preoperative pain (OR 1.21 [95% CI 1.10 to 1.32]) and use of preoperative analgesia (OR 1.54 [95% CI 1.18 to 2.03]). Pooled ORs and definition for each preoperative variable are given in table 2. Summary forest plots of significant preoperative predictors of poor postoperative pain control are shown in figure 3. Significant heterogeneity was detected in five 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 supplementary figures S1–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, orthopaedic surgery compared with abdominal surgery, diabetes, pain catastrophising as a continuous variable, higher education, age as a continuous variable, chronic pain, American Society of Anesthesiologists 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 supplementary figures S4–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, generalised 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 anaemia, anticonvulsant medication, home sedatives, electrical pain threshold, heat pain threshold, von Frey pain intensity, blood type, preoperative 24 hours urinary cortisol level, thoracic surgery, spine surgery, head and 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

Table 1 Study characteristics of included studies

Author, year	Country of origin	Sample size	Incidence of poor postoperative pain control (%)	Mean age in years (SD)	Study design	Setting of pain assessment	Pain scale*	Definition of poor pain control	Time of assessment†	Specialty	Pathology	No. of predictors examined
Alves <i>et al.</i> , 2013 ³⁹	Brazil	139	Not stated	51.7 (11.8)	PCS	Ward	VAS	>30	24	GS	Breast cancer	3
Auburn <i>et al.</i> , 2008 ⁴⁰	France	342	41.5	48 (18)	PCS	PACU	VAS and NRS	Morphine>0.15mg/kg in PACU	<24 hours	Mixed	Mixed	3
Baudic <i>et al.</i> , 2016 ⁴¹	France	100	14.0	55.2 (12.1)	PCS	Ward	BPI	≥3	48	GS	Breast cancer	9
Beli <i>et al.</i> , 2014 ⁴²	Moldova	176	Not stated	Not stated	PCS	Ward	NRS	≥5	24	GS	Abdominal pathologies	3
Borges <i>et al.</i> , 2016 ⁴³	Brazil	1062	78.4	25.1 (5.7)	PCS	Ward	NRS	≥5	Immediate postoperative period	Obstetric	Non-emergent caesarean section	14
Camuo <i>et al.</i> , 2002 ⁴⁴	Brazil	346	43.4	44.3 (9.6)	PCS	PACU	VAS	>30	24	GS	Abdominal pathologies	15
Duan <i>et al.</i> , 2017 ⁴⁵	China	1002	15.5	49.5 (11.6)	PCS	Ward	NRS	≥4	24	Mixed	Mixed	3
Genov <i>et al.</i> , 2015 ⁴⁶	Russia	321	Not stated	Not stated	RCS	PACU	VAS	>4	12	Mixed	Mixed	1
Gaerbershagen <i>et al.</i> , 2014 ⁴⁷	Germany	22 963	24.5	55.2‡	PCS	Ward	NRS	≥7	24	Mixed	Mixed	3
Gorkem <i>et al.</i> , 2016 ⁴¹	Turkey	80	Not stated	29.7 (5.8)	PCS	Ward	VAS	>40	18	Obstetric	Non-emergent caesarean section	16
Jae Chul <i>et al.</i> , 2015 ⁵²	Korea	10 575	Not stated	Young: 31.8 (5.8) Old: 74.8 (4.4)	RCS	Ward	NRS	>4	48	Mixed	Mixed	5
Jasim <i>et al.</i> , 2017 ⁴⁸	Malaysia	400	Not stated	30.4 (4.8)	RCS	PACU and Ward	VAS	Not stated	12	Obstetric	Non-emergent caesarean section	7
Katz <i>et al.</i> , 2005 ²²	USA	109	54.1	58.2 (12)	PCS	Ward	NRS	≥5	48	GS	Breast cancer	17
Kim <i>et al.</i> , 2016 ⁴⁹	UK	156	42.3	64.4 (10.9)	PCS	Ward	NRS	≥5	48	GS	Gastric tumours (endoscopic resection)	11
Lesin <i>et al.</i> , 2016 ⁵⁰	Croatia	226	19.9	67 (13)	PCS	Ward	NRS	≥5	6	Ophtho	Ophthalmologic pathologies	19
Liu <i>et al.</i> , 2012 ²³	USA	897	At rest: 22.4 Movement: 39.0	67 (11)	RCS**	Ward	NRS at rest & with activity	>4	24	Orthopaedic	Primary total hip or knee replacement	17
Lunn <i>et al.</i> , 2013 ⁵¹	Denmark	92	39.1	Median 66 (IQR 13)	PCS	Ward	VAS (with activity)	≥60	6–24	Orthopaedic	Total knee arthroplasty	4
Mamie <i>et al.</i> , 2004 ⁵²	Switzerland	304	25.1	45‡	PCS	Ward	VAS	>5	24	Mixed	Abdominal and orthopaedic pathologies	10
Mei <i>et al.</i> , 2010 ⁵³	Germany	1736	28.5	Not stated	PCS	PACU	NRS	>4	After extubation	Mixed	Mixed	10
Murray <i>et al.</i> , 2016 ⁵⁴	South Africa	1231	61.9	44¶	PCS	Ward	VAS	>40	24	Mixed	Mixed	8
Nishimura <i>et al.</i> , 2017 ²⁴	Japan	64	48.4	60 (11)	PCS	Ward	VAS	>40	6–60	GS	Partial mastectomy for cancer	8
Orbach-Zinger <i>et al.</i> , 2017 ⁵⁵	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 caesarean section	3
Persson <i>et al.</i> , 2017 ⁵³	Sweden	152	Not stated	Median 49 (IQR 29)	PCS	PACU	VAS	>40	1.5	GS	Laparoscopic cholecystectomy	2

Continued

Table 1 Continued

Author, year	Country of origin	Sample size	Incidence of poor postoperative pain control (%)	Mean age in years (SD)	Study design	Setting of pain assessment	Pain scale*	Definition of poor pain control	Time of assessment†	Specialty	Pathology	No. of predictors examined
Petrovic <i>et al.</i> , 2014 ⁵⁶	Serbia	90	48.9	High pain group: 64.2 (3.8) Low pain group: 69 (3.9)	PCS	Ward	NRS	≥5	12	Orthopaedic	Total hip arthroplasty	15
Radinovic <i>et al.</i> , 2014 ⁵⁷	Serbia	234	Not stated	71.2 (6.3)	PCS	PACU	NRS	≥7	1	Orthopaedic	Hip fractures	14
Rakel <i>et al.</i> , 2012§ ³⁴	USA	215	Moderate pain: 46.0 Severe pain: 27.0	61.7 (9.8)	PCS	Ward	NRS (0–21)	8–14 (moderate) 15–20 (severe)	48	Orthopaedic	Total knee arthroplasty	17
Rehberg <i>et al.</i> , 2017 ¹⁹	Switzerland	198	44.9	57.5 (12.5)	PCS	Ward	NRS	>3	24	GS	Breast cancer	15
Robleda <i>et al.</i> , 2014 ³⁸	Spain	127	61.0	71.0 (18)	RCS	PACU	NRS	≥4	Immediate in PACU	Orthopaedic	Femur fractures and prosthetics	15
Sanansip <i>et al.</i> , 2016 ⁵⁹	Thailand	340	28.5	54.8 (17.8)	PCS	Ward	NRS	≥4	24–48	Mixed	Mixed	12
Sommer <i>et al.</i> , 2010 ⁶⁰	Netherlands	1300	30.2	56 (15.5)	PCS	Ward	VAS	>40	24	Mixed	Mixed	15
Storesund <i>et al.</i> , 2016 ⁶¹	Norway	336	67.3	52 [¶]	RCS**	PACU	VAS or vNRS	≥4	At the time of transfer out of PACU	Orthopaedic	Ankle fractures	15
Tighe <i>et al.</i> , 2014 ⁶²	USA	7731	60.9	Female: 56.4 [¶] Male: 56.6 [¶]	RCS	Ward	NRS	≥7	24	Mixed	Mixed	1
Zhao <i>et al.</i> , 2014 ⁶³	China	73	58.9	Median 43 (IQR 57)	PCS	PACU and Ward	VAS	>30	24	GS	Haemorrhoids	12

*Pain measured at rest, unless otherwise stated.

†Time of assessment measured in hours.

‡Authors' estimate (study only included age ranges).

§Studies that divided their data set into two groups when evaluating predictors: Jae Chul *et al.*: young versus old age group; Liu *et al.*: NRS at rest versus with activity; Persson *et al.*: female versus male and Rakel *et al.*: moderate versus severe pain outcome.

¶Variance not stated.

**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); GS, general surgery; Mixed, more than one specialty or pathology; NRS, numeric rating scale for pain (0–10); PCS, prospective cohort study; RCS, retrospective cohort study; VAS, visual analogue scale for pain (0–100 mm); vNRS, verbal numeric rating scale for pain (0–10); PACU, Post-anesthesia care unit.

	1	2	3	4	5	6	7	8	9
Alves 2013	+	+	+	+	?	-	+	+	+
Auburn 2008	+	?	+	+	?	-	+	+	+
Baudic 2016	+	+	+	-	?	+	+	+	+
Belli 2014	+	+	+	+	?	-	+	+	+
Borges 2016	+	+	-	+	?	-	+	+	+
Camuo 2012	+	+	+	+	+	+	+	+	+
Duan 2017	+	?	+	+	?	+	+	+	+
Genov 2015	+	+	+	+	+	+	+	+	+
Gerbershagen 2014	+	+	+	+	+	-	+	+	+
Gorkem 2016	+	+	-	+	+	+	+	+	+
Jae Chul 2015	+	+	+	+	-	+	+	+	+
Jasim 2017	+	+	+	+	?	+	+	-	+
Katz 2005	+	+	+	+	?	+	+	+	+
Kim 2016	+	+	+	+	?	-	+	+	+
Lesin 2016	+	?	+	+	?	+	+	+	+
Liu 2012	+	+	+	+	?	+	+	+	+
Lunn 2013	+	+	+	+	+	+	+	+	+
Mamie 2004	+	+	-	+	+	+	+	+	+
Mei 2010	+	+	+	+	?	+	+	+	+
Murray 2016	+	+	+	+	?	+	+	+	+
Nishimura 2017	+	+	+	+	?	-	+	+	+
Orbach-Zinger 2016	+	+	+	+	?	+	+	+	+
Persson 2017	+	+	+	+	?	+	+	+	+
Petrovic 2014	+	+	-	+	?	+	+	+	+
Radnovic 2014	+	+	+	+	?	+	+	+	+
Rakel 2012	+	+	+	+	?	-	+	+	+
Rehberg 2017	+	+	+	+	+	+	+	+	+
Robleda 2014	+	?	?	+	?	-	+	+	+
Sananslip 2016	+	+	+	+	?	+	+	+	+
Sommer 2010	+	+	+	+	+	+	+	+	+
Storesund 2016	+	+	+	+	?	+	+	+	+
Tighe 2014	+	+	+	+	?	-	+	+	+
Zhao 2014	+	+	+	+	?	-	+	+	+

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 and red: high risk of bias.

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 nine 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 twofold higher odds of poor postoperative pain control. Our findings are consistent with and extend the results of the previous systematic review by Ip

*et al.*²⁰ In addition to the predictors previously described, we identified six additional preoperative predictors of poor postoperative pain control.²⁰

Previous reports have been inconsistent in their conclusions regarding the association of female sex with worse pain prognosis after surgery.^{20 60} Some have observed higher pain scores in females,^{47 50 53 54} whereas others failed to find such a difference between sexes.^{34 57 59} In this meta-analysis, we found females had an approximately 30% increased odds of poor postoperative pain control compared with males. Sex differences may potentially relate to complex psychosocial and biological factors, such as an increased willingness of women to communicate pain,⁶⁴ and subjective differences in pain perception and experience.²⁰ Indeed, females are reported to require 11% greater doses of morphine on average compared with males in order to achieve adequate postoperative analgesia.⁶⁵ 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 (eg, 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 individualise 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.^{66 67} 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 programmes 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.⁴⁴ 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.^{23 68} This may be due to greater preoperative severity of pain, opioid-induced hyperalgesia and central or peripheral sensitisation to pre-existing nociception.^{23 69} Further research on the impact of modifying these risk factors in the preoperative

Table 2 Pooled ORs and definitions of preoperative predictors of poor postoperative pain control

Preoperative predictor	No. of studies included in the pooled estimate	No. of patients	OR (95% CI)	P value	I ² statistic	Definition
Younger age	14	5577	1.18 (1.05 to 1.32)	<0.001	79.7%*	Authors' cut-off (range ≤31 to <70 years)
Female sex	20	48753	1.29 (1.17 to 1.43)	<0.001	71%*	Female sex
Smoking	9	15764	1.33 (1.09 to 1.61)	0.005	55.8%*	Self-reported (any amount)
History of depressive symptoms	8	3042	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 and Geriatric Depression Scale >6)
History of anxiety symptoms	10	2598	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 and 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 Pittsburgh Sleep Quality Index
BMI (continuous)	2	1095	1.02 (1.01 to 1.03)	<0.001	0%	BMI as a continuous variable
Presence of preoperative pain	13	4733	1.21 (1.10 to 1.32)	<0.001	50.4%*	Self-reported, any preoperative pain
Preoperative analgesia use	6	2448	1.54 (1.18 to 2.03)	0.002	44.0%	Self-reported use of preoperative analgesia or opioids
Age (continuous)	9	26846	0.97 (0.93 to 1.01)	0.16	93.5%*	Age as a continuous variable
Higher education	8	2272	0.97 (0.69 to 1.38)	0.89	43.4%	Authors' cut-off from self-reported levels of education (range: >9 years of education to college or postgraduate degree)
History of surgery	8	3954	1.15 (0.97 to 1.37)	0.10	33.9%	Any self-reported previous surgical history
Alcohol use	5	3851	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	3629	0.94 (0.59 to 1.51)	0.80	79.0%*	ASA I compared with II or III
High BMI (dichotomous)	5	1926	1.23 (0.98 to 1.55)	0.069	66.5%*	Authors' cut-off (range from >30 to >40 kg/m ²)
Chronic pain	4	1583	0.96 (0.65 to 1.42)	0.84	59.5%	Self-reported chronic pain
Diabetes	4	1287	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	1571	1.42 (0.62 to 3.23)	0.41	60.1%	Self-reported as single or not married
Orthopaedic procedure	3	10879	1.06 (0.72 to 1.57)	0.77	76.3%*	Orthopaedic procedure compared with abdominal surgery

Continued

Table 2 Continued

Preoperative predictor	No. of studies included in the pooled estimate	No. of patients	OR (95% CI)	P value	I ² statistic	Definition
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 Gauge FPX 50 or hand-held pressure algometer (Somedic AB, Farsta, Sweden)
Low socioeconomic status	2	1288	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 US\$750
Pain Catastrophizing Scale (dichotomous)	2	1476	1.47 (0.67 to 3.22)	0.34	73.0%	Authors' cut-off (range from \geq or >15)

*Significant Cochran's Q test ($p < 0.05$).
 ASA, American Society of Anesthesiologists; BMI, body mass index.

and perioperative period is needed to determine its effect on improving postoperative pain outcomes.

Strengths and 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 generalisability 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 categorise continuous preoperative predictors between studies (eg, 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 standardise definitions (common data elements) to facilitate comparisons between studies. For significant predictors that were evaluated by a limited number of studies (eg, 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

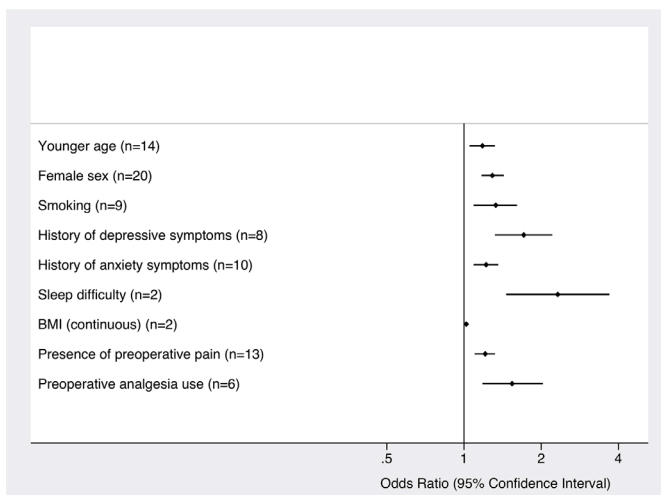


Figure 3 Summary forest plot for significant preoperative predictors of poor postoperative pain control. ORs are shown with 95% CIs. The number of studies included in the meta-analysis for each predictor is indicated. BMI, body mass index.

case-mix. Additional research may further define the influence of specific types of surgery on pain control.

CONCLUSION

In conclusion, we identified and described nine 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 individualised interventions, better pain management and decrease reliance on pain medications (particularly opioids). Increased awareness of these predictors can also aid in the development of personalised discipline-specific clinical care pathways (eg, multimodal analgesic strategies and enhanced recovery after surgery programmes) to reduce the 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, which 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, multicentre 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.

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