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Persistent Incisional Pain after Noncardiac Surgery: An International Prospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Persistent pain after surgery is common, limits functional recovery, and contributes to psychologic distress
- Most studies examining persistent postoperative pain have been small and involved limited time frames

What This Article Tells Us That Is New

- Incisional pain persisting for up to 1 yr after major noncardiac surgery was assessed prospectively in a cohort of more than 14,000 patients
- Persistent incisional pain was identified in 3.3% of the patients, with nearly half reporting moderate to severe pain
- Several risk factors, including female sex, history of chronic pain, coronary heart disease, and others, were identified

ABSTRACT

Background: The purpose of this study was to determine the incidence, characteristics, impact, and risk factors associated with persistent incisional pain. The hypothesis was that patient demographics and perioperative interventions are associated with persistent pain.

Methods: This was a secondary analysis of an international prospective cohort study from 2012 to 2014. This study included patients who were 45 yr of age or older who underwent major inpatient noncardiac surgery. Data were collected perioperatively and at 1 yr after surgery to assess for the development of persistent incisional pain (pain present around incision at 1 yr after surgery).

Results: Among 14,831 patients, 495 (3.3%; 95% CI, 3.1 to 3.6) reported persistent incisional pain at 1 yr, with an average pain intensity of 3.6 ± 2.5 (0 to 10 numeric rating scale), with 35% and 14% reporting moderate and severe pain intensities, respectively. More than half of patients with persistent pain reported needing analgesic medications, and 85% reported interference with daily activities (denominator = 495 in the above proportions). Risk factors for persistent pain included female sex ($P = 0.007$), Asian ethnicity ($P < 0.001$), surgery for fracture ($P < 0.001$), history of chronic pain ($P < 0.001$), coronary artery disease ($P < 0.001$), history of tobacco use ($P = 0.048$), postoperative patient-controlled analgesia ($P < 0.001$), postoperative continuous nerve block ($P = 0.010$), insulin initiation within 24 h of surgery ($P < 0.001$), and withholding nonsteroidal anti-inflammatory medication or cyclooxygenase-2 inhibitors on the day of surgery ($P = 0.029$ and $P < 0.001$, respectively). Older age ($P < 0.001$), endoscopic surgery ($P = 0.005$), and South Asian ($P < 0.001$), Native American/Australian ($P = 0.004$), and Latin/Hispanic ethnicities ($P < 0.001$) were associated with a lower risk of persistent pain.

Conclusions: Persistent incisional pain is a common complication of inpatient noncardiac surgery, occurring in approximately 1 in 30 adults. It results in significant morbidity, interferes with daily living, and is associated with persistent analgesic consumption. Certain demographics, ethnicities, and perioperative practices are associated with increased risk of persistent pain.

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Surgery appears to be a major cause of chronic pain, as 22% of patients seeking care at a chronic pain clinic attribute their pain to a surgical procedure.[1] Persistent postsurgical pain has been defined as the presence of pain after the usual healing time of surgery (3 months), localized to the surgical incision or referred pattern of pain (*e.g.*, along a nerve distribution or dermatome), and not due

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to any organic cause of pain (*i.e.*, infection, malignancy).[2] Because chronic pain is often refractory to treatment, efforts have been directed toward identifying preventative therapies within the perioperative period.[3] Unfortunately, no definitive interventions have been identified, and chronic postsurgical pain continues to be a significant source of long-term physical, psychologic, emotional, and social distress.[4] Chronic pain contributes to concurrent depression and anxiety, and 10% of patients with chronic pain will attempt suicide.[5–9] Economic hardships are common in those with chronic pain due to disability and reduced work productivity.[10] Additionally, chronic opioid use is associated with long-term morbidities (overdose, tolerance, hyperalgesia), and surgery and trauma are responsible for chronic opioid use in 2.6% of opioid-naïve adults.[11]

Although surgery is known to be a trigger for chronic pain, there is substantial variation in the reported incidences of persistent pain after noncardiac surgery. The majority of studies have been conducted within specific surgical populations and provide estimates ranging from 0 to 60%.[12,13] Variation is likely due to a number of factors including differences in regional surgical and perioperative practices, small sample sizes (100 to 300 patients), time of outcome assessment after surgery, and inconsistent definitions.[2]

Using data from a large, international, prospective cohort study (the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation [VISION] Study; clinicaltrials.gov identifier NCT00512109), we aimed to identify the incidence, characteristics, impact, and risk factors associated with the development of persistent incisional pain after noncardiac surgery. Our hypotheses for this analysis were that demographics and perioperative pain interventions would influence the risk of developing persistent pain.

Materials and Methods

The VISION Study

VISION was an international, prospective cohort study of 40,004 patients who underwent noncardiac surgery between August 2007 and February 2014 in 28 centers in North and South America, Africa, Asia, Australia, and Europe.[14] The primary aim of VISION was to determine the incidence of myocardial injuries and major vascular complications after noncardiac surgery. During the conduct of VISION, we developed a substudy to evaluate persistent incisional pain at 1 yr after surgery. This substudy and accompanying data collection started in June 2012 and included all patients that were alive and able to provide 1-yr follow-up data.

Eligible patients were identified by screening daily patient lists (in preoperative assessment clinics, surgical wards, and intensive care units), screening daily and previous-day surgical lists, and assessing patients in the preoperative holding area on the day of surgery. Patients provided written informed consent to participate in the study (VISION) and associated substudies before undergoing surgery. For those unable to provide consent before surgery (*i.e.*, emergency surgery), consent was obtained within 24 h after surgery. Eight centers used a deferred consent process for patients unable to provide consent (*e.g.*, patients who were sedated or mechanically ventilated) when no next of kin was available.

Patients were included into VISION if they were 45 yr of age or more, had noncardiac surgery, and received a general or regional anesthetic. Patients were excluded from the study if they did not require at least an overnight hospital admission after surgery, received only local infiltration (*i.e.*, local anesthesia), were previously enrolled in VISION, or did not provide informed consent. Research ethics board/institutional review board approval was obtained from each participating site. Details on patient enrollment, data collection, and follow-up in VISION has been published previously.[14]

At the time of enrollment, patient information was collected including demographics, past medical history, medications, indications for surgery, and history of chronic pain. Research personnel also collected information regarding the type of surgery, anesthetic technique, and perioperative medications. At the 1-yr follow-up, the diagnosis of persistent incisional pain was made by asking patients about the presence of pain localized to their surgical incision that was not present before surgery or caused by any other known cause such as infection or malignancy. This assessment was typically performed *via* a telephone follow-up interview. Those who reported the presence of persistent pain were further assessed for neuropathic pain characteristics, use of pain medications, severity of pain at its worst and least, average pain (over the last 24 h), pain at time of interview using the numeric rating scale (0 to 10, where 0 is no pain and 10 is worst possible pain), interference of pain on aspects of daily living, whether an analgesic medication was used to manage their pain (did not specify whether opioid or nonopioid analgesic), and neuropathic pain characteristics. Assessment of neuropathic pain characteristics was performed by asking patients to gently rub the skin around their surgical incision and rate the presence of neuropathic characteristics (*e.g.*, tingling, numbness, increased pain caused by light touch [allodynia]) using a 0 to 10 scale. Research personnel at each site submitted patient data on case report forms directly to an online data management system (iDataFax, McMaster University, Hamilton, Ontario, Canada). Data monitoring occurred through the use of iDataFax data system checks, statistical monitoring, and on-site monitoring for all participating centers.

Statistical Analysis

An *a priori,* written, date-stamped (November 14, 2018) statistical analysis plan was recorded in the investigators' files before accessing the study data. All patients who were asked about persistent incisional pain at the 1-yr follow-up were

included in our analysis. We expressed the incidence of persistent incisional pain, across all patients and per specific surgery subgroup, as a percentage of patients affected over the total number of patients at follow-up assessed with a 95% CI. We reported the mean and SD of continuous variables and the number of occurrences with proportions represented as percentages for categorical variables (neuropathic pain features, interference on aspects of daily living, those taking a medication to treat their pain). We also reported those who were taking a medication to treat their pain at 1 yr and then identified the level of interference between those who were and were not taking a pain medication.

We conducted univariate analyses on baseline patient demographics between the entire sample and those reporting persistent pain (table 1), using a *t* test for continuous variables and chi-square test for categorical variables. Two separate multivariable logistic regression models were planned *a priori* to identify preoperative and perioperative risk factors associated with the development of persistent incisional pain. Variables chosen for inclusion in these models were selected *a priori* based on clinical suspicion and biologic plausibility (described in our statistical analysis plan). Preoperative variables included patient demographics (*i.e.*, age [in decades], sex, body mass index, ethnicity [eight categories], comorbidities [*i.e.*, a history of diabetes, chronic pain, tobacco use, coronary artery disease, peripheral vascular disease, or active cancer]) and indications for surgery (*i.e.*, surgery for fracture). We defined a preoperative history of chronic pain as daily pain for 3 months or more during which patients were taking one more of the following pain medications daily: tricyclic antidepressants, anticonvulsants, or opioids other than codeine. Perioperative variables included preoperative medications (*i.e.*, aspirin, insulin, oral hypoglycemic drugs, cyclooxygenase-2 inhibitors, nonsteroidal anti-inflammatories) taken within 24 h and the previous 7 days, within 24 h only, and within 7 days only but not within 24 h before surgery; intraoperative anesthetic technique (*i.e.*, spinal or epidural anesthesia, regional anesthetic block, use of nitrous oxide); postoperative pain management modalities (*i.e.*, epidural, patient-controlled analgesia [PCA], postoperative continuous nerve block, intramuscular or intravenous opioids); and whether the surgery was open or endoscopic. We excluded independent variables with fewer than 50 observations per category unless we were able to collapse them with other related variables to exceed this threshold. The dependent variable in both models was persistent incisional pain at 1 yr after surgery. The number of variables included in the model was limited to the number of events of incisional pain using a ratio of 10 events for every variable included to ensure model stability and reduce overfitting.[15] All variables were included into the model using forced simultaneous entry, and the reported estimates were adjusted (controlling for other variables in the model) to identify the independent effects of each variable. We tested for collinearity using the variance inflation factor, and if two variables were highly correlated (a variance inflation factor greater than 5), the least significant variable (lower coefficient) was dropped from the model.[16] The goodness of fit of the logistic regression models was assessed using the Hosmer–Lemeshow test.[17] Missing data were handled by using only cases with complete data.

We reported adjusted odds ratios along with their 95% CIs for all independent factors assessed in our regression models including absolute risk increase or reductions for each significant predictor. Baseline risk for persistent postsurgical incisional pain was determined by calculating the

Table 1. Patient Characteristics of Total Sample and Those with Persistent Incisional Pain

Variables	Total Sample (n = 14,831)	Persistent Incisional Pain (n = 495)
Mean age (SD), yr	68.7 (10.9)	66.3 (10.2)*
Sex, male/female, no. (%)	7,288 (49.1)/7,543 (50.9)	209 (42.2)/286 (57.8)*
Mean body mass index, kg/m^2 (SD)	27.8 (7.9)	28.3 (6.9)
Diabetes, no. (%)	3,030 (20.4)	102 (20.6)
Active cancer, no. (%)	2,081 (14.0)	60 (12.1)
History of tobacco use, no. (%)	6,076 (41.0)	239 (48.3)*
Coronary artery disease, no. (%)	1,705 (11.5)	83 (16.8)*
Peripheral vascular disease, no. (%)	791 (5.3)	32 (6.5)
History of chronic pain, no. (%)	1,500 (10.1)	109 (22.0)*
Surgeries, no (%)		
General surgeries	2,936 (19.1)	97 (19.6)
Orthopedic surgeries	2,793 (18.8)	143 (28.9)*
Urologic–gynecologic surgeries	2,156 (14.5)	36 (7.3)*
Neurosurgery	817 (5.5)	47 (9.5)*
Vascular surgery	700 (4.7)	18 (3.6)
Thoracic surgery	287 (1.9)	14 (2.8)
Head and neck surgeries	189 (1.3)	7 (1.4)
Other surgery	5,500 (37.1)	152 (30.7)*

*$P < 0.05$ for between-group differences

incidence among surgical patients with removing major significant risk factors. No sample size calculation was performed before this study because it was primarily exploratory in nature and based on available data.

Two *post hoc* sensitivity analyses were conducted. The first sought to assess the potential impact of missing data on the estimate of persistent incisional pain at 1 yr. Multiple imputation was performed across 20 iterations to impute pain data for patients who were missing at 1 yr after surgery. Available baseline data (*i.e.*, *a priori* variables selected to be included in the multivariable regression models and surgical categories) were used in the regression model to impute missing data. Incidence of persistent incisional pain was averaged across the 20 iterations to identify a pooled incidence and 95% CI. The second sensitivity analysis sought to confirm the results of our individual preoperative and perioperative multivariable regression models by constructing a single model that included all predictors in addition to surgical groups (eight categories). All statistical analyses were performed using SPSS (USA) version 10 software. All tests were two-sided, and significance was defined as $P < 0.05$.

Results

The primary study (VISION) enrolled 40,037 patients of which 33 were excluded from the cohort (fig. 1). At the 1-yr follow-up, 1,353 patients had died, and 6,080 patients were unable to be contacted for follow-up data. Because pain outcomes were only introduced in 2012 (5 yr after the start of the study), 17,740 patients were never asked about pain at their 1-yr follow-up. This resulted in a total of 14,831 patients who were alive and who provided data on persistent pain at the 1-yr point (fig. 1).

The mean age of patients included in the analysis was 68.7 ± 10.9 yr old, 51% were female, 20% had a history

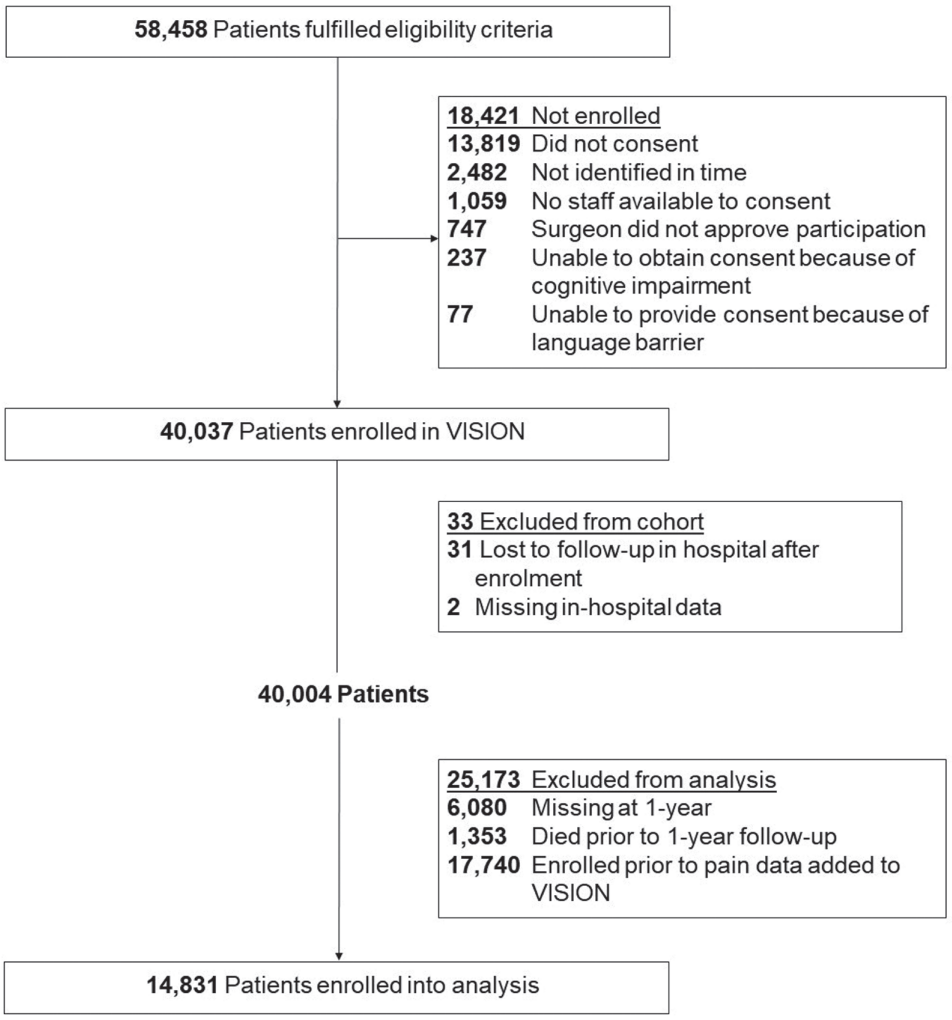

Fig. 1. Patient flow diagram. VISION, Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study.

of diabetes, 14% had active cancer, and 41% had a history of tobacco use. Approximately 10% of patients reported chronic pain before surgery. The most common procedures were general surgery (19.1%), orthopedic surgery (18.8%), and urologic–gynecologic surgery (14.5%; table 1).

At 1 yr, 495 patients (3.3%; 95% CI, 3.1 to 3.6%) reported persistent incisional pain. In the univariate analysis (table 1), compared to the entire sample, those with persistent pain were significantly younger; included more females; had a higher rate of tobacco use, coronary artery disease, and history of chronic pain; and had undergone more orthopedic and neurosurgeries and fewer urologic–gynecologic surgeries and other surgeries. The incidence of incisional pain varied across type of surgical subgroups (fig. 2). Pneumonectomies had the highest rate (7.1%) followed by major spine surgery (6.2%), complex visceral resections (6.1%), thoracic aortic reconstructions (5.7%), and other thoracic surgery (5.5%). The incidence of persistent pain in those with a history of chronic pain was 7.3% (95% CI, 6.0 to 8.7%), and those without chronic pain had an incidence of 2.9% (95% CI, 2.6 to 3.2%).

Among participants with persistent incisional pain at 1-yr follow-up, in the previous 24 h, the worst pain was on average 5.1 ± 2.7, least pain was 2.0 ± 2.3, pain on average was 3.6 ± 2.5, and pain at time of interview was 2.7 ± 2.7 (table 2). With regards to pain intensities over the past 24 h, 51.5% reported mild pain (pain scores 0 to 3), 34.9% reported moderate pain (pain scores 4 to 6), and 13.6% reported severe pain (pain scores 7 to 10; tables 2 and A1). Furthermore, 81% of patients reported one or more features of neuropathic pain characteristics (*i.e.*, tingling, numbness, or allodynia associated with touch around their surgical scar); specifically, 39.6% of patients with incisional pain reported tingling, 47.1% reported numbness, and 57.4% reported allodynia (table A2).

Most patients (85.1%) reported interference of pain on some aspect of their daily living, with the majority of patients reporting some level of interference on specific activities (table 3). The highest interference was reported with walking (scale 0 to 10: 3.5 ± 3.7), normal work (3.5 ± 3.4), and general activity (3.4 ± 3.3). Specifically, with respect to interference on general activities, 33.5% reported no interference, 22.2% reported mild interference, 22.5% reported moderate interference, and 21.7% reported severe interference.

Approximately 52.7% of patients with persistent incisional pain reported taking a pain medication specifically

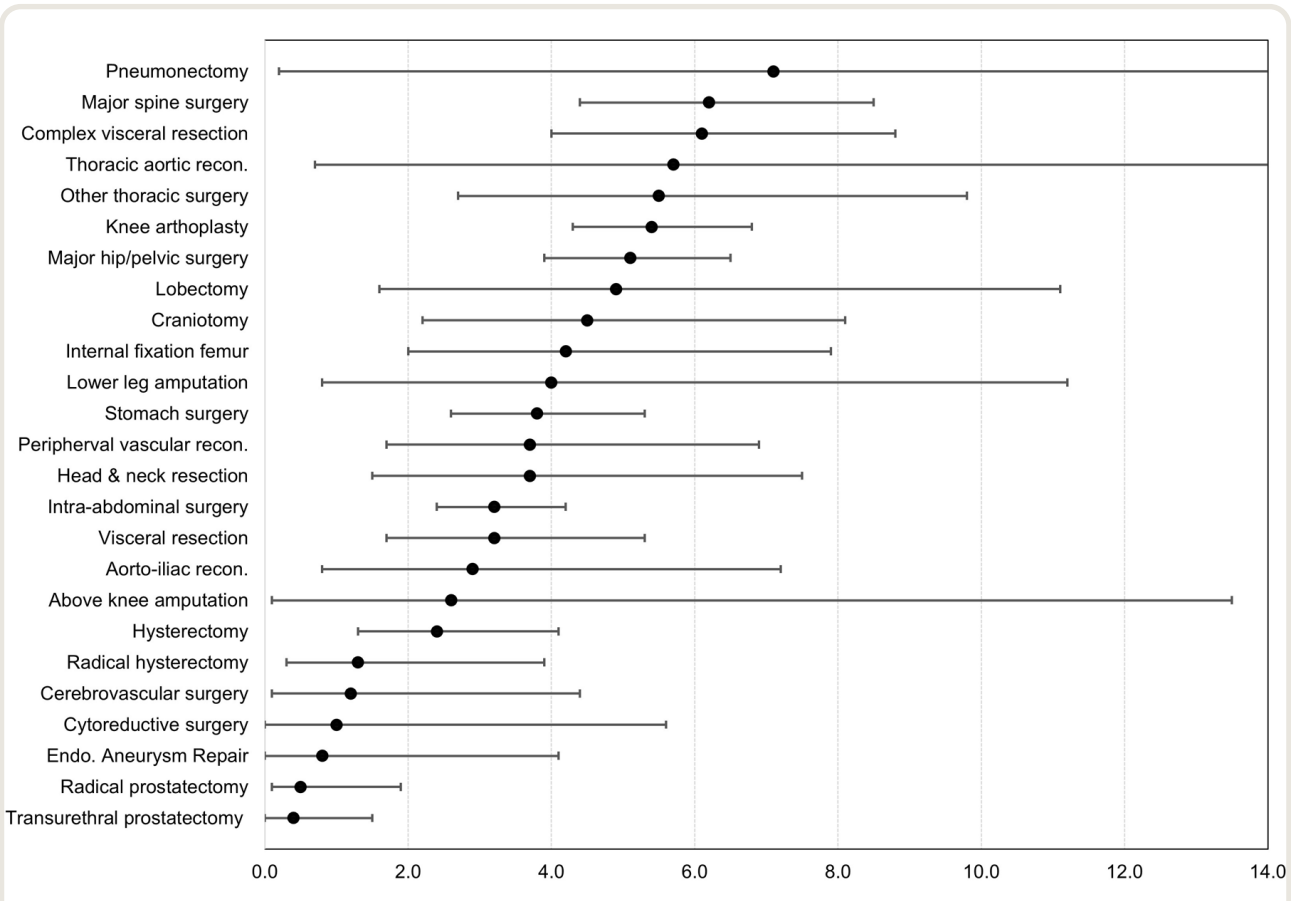

Fig. 2. Incidence of persistent incisional pain in specific surgical populations. *Error bars* indicate 95% CI.

Table 2. Pain Intensities Associated with Persistent Incisional Pain (n = 495)

Pain Scores	Values
Mean (SD)	
Worst pain (last 24 h)	5.1 (2.7)
Least pain (last 24 h)	2.0 (2.3)
Average pain (last 24 h)	3.6 (2.5)
Pain intensity now (at time of follow-up)	2.7 (2.7)
No., %	
Mild pain (pain scores 0 to 3)	251 (51.5)
Moderate pain (pain scores 4 to 6)	170 (34.9)
Severe pain (pain scores 7 to 10)	66 (13.6)

Pain scores indicate the patient rating of pain on a numeric rating scale from 0 to 10.

for relief of their incisional pain. Those taking a pain medication suffered significantly greater interference on all aspects of daily living (all $P < 0.001$) compared to those who were not taking pain medication for their incisional pain (table A3).

In the multivariable logistic regression model of preoperative risk factors associated with the development of persistent incisional pain, nine independent predictors were identified: Asian ethnicity (odds ratio, 2.98; 95% CI, 2.36 to 3.76; $P < 0.001$), history of chronic pain (odds ratio, 2.29; 95% CI, 1.82 to 2.88; $P < 0.001$), surgery for fracture (odds ratio, 2.08; 95% CI, 1.43 to 3.02; $P < 0.001$), history of coronary artery disease (odds ratio, 1.89; 95% CI, 1.44 to 2.47; $P < 0.001$), female sex (odds ratio, 1.32; 95% CI, 1.08 to 1.61; $P = 0.007$), history of tobacco use (odds ratio, 1.23; 95% CI, 1.0 to 1.52; $P = 0.048$), age (odds ratio, 0.71 [per decade]; 95% CI, 0.65 to 0.78; $P < 0.001$), South Asian ethnicity (odds ratio, 0.315; 95% CI, 0.210 to 0.473; $P < 0.001$), Native American/Australian ethnicity (odds ratio, 0.303; 95% CI, 0.134 to 0.686; $P = 0.004$), and Latin/Hispanic ethnicity (odds ratio, 0.152; 95% CI, 0.080 to 0.289; $P < 0.001$; table 4).

In the multivariable logistic regression model of perioperative interventions to predict the development of persistent incisional pain at 1 yr after surgery, six variables were found to be significantly associated (table 5). Only one of these variables were associated with a lower risk of persistent pain, which was endoscopic surgery (odds ratio, 0.71; 95% CI, 0.56 to 0.90; $P = 0.005$). Five variables were associated with increased risk of pain, including (in order of increasing risk): NSAIDs taken 1 to 7 days before surgery but stopped within 24 h of surgery (odds ratio, 1.55; 95% CI, 1.05 to 2.30; $P = 0.029$); postoperative PCA use (odds ratio, 1.92; 95% CI, 1.57 to 2.34; $P < 0.001$); postoperative continuous nerve block use (odds ratio, 2.27; 95% CI, 1.21 to 4.24; $P = 0.010$); cyclooxygenase-2 inhibitors taken 1 to 7 days before surgery but stopped within 24 h of surgery (odds ratio, 2.59; 95% CI, 1.66 to 4.07; $P < 0.001$); and insulin not taken within 1 to 7 days of surgery but given within 24 h of surgery (odds ratio, 3.02; 95% CI, 1.82 to 5.00; $P < 0.001$).

The *post hoc* sensitivity analysis on missing data indicated that the incidence of persistent pain may be slightly higher (3.7%; 95% CI, 3.2 to 4.2%) than our observed incidence rate. The second sensitivity analysis confirmed the significance of all predictors identified in the separate preoperative and perioperative regression models except for endoscopic surgery ($P = 0.076$), history of tobacco use (0.058), and postoperative continuous nerve block ($P = 0.127$; table A4).

Table 3. Interference of Pain on Aspects of Daily Activities in Patients with Persistent Incisional Pain (n = 495)

Daily Activity	No. (%)	Scale 0 to 10, mean (SD)*
General activity	325 (66.5%)	3.4 (3.3)
Normal work	323 (66.3%)	3.5 (3.4)
Walking activity	315 (64.5%)	3.5 (3.7)
Mood	297 (61.0%)	2.9 (3.1)
Sleep	294 (60.4%)	3.0 (3.3)
Enjoyment of life	284 (58.2%)	2.8 (3.2)
Relations with other people	202 (41.5%)	2.0 (2.9)

*Patients reporting some level of interference.

Discussion

In this secondary analysis of a large, international, representative sample of patients who underwent inpatient noncardiac surgery between 2012 and 2014, approximately 1 in 30 patients reported persistent incisional pain 1-yr after their surgery. Persistent incisional pain is associated with mild-to-moderate pain intensity, neuropathic pain features, interference with aspects of daily living, and persistent analgesic use.

The incidence of persistent incisional pain in our study (3.3%) is lower than most estimates reported in the literature. Although most investigations on persistent pain after surgery have been conducted within specific surgical subgroups, previous studies that included a noncardiac surgical cohort have reported rates greater than 10% at 1 yr postoperatively.[18–20] Several reasons may explain differences between our findings and previous investigations. First, many previous studies have typically not specified the location of persistent pain, whereas our investigation focused on pain around the incisional.[21] For example, persistent pain after breast cancer surgery presents with pain in the chest wall, medial arm, shoulder, or axilla and not necessarily pain at the incision site.[22,23] Similarly, only 15% of patients with persistent pain after inguinal hernia repair report pain in the area of surgery.[24] Second, differences in postoperative follow-up times for outcome assessment after surgery has a drastic impact on the incidence rate detected.[25] For example, in the same cohort of patients who had radical prostatectomies, the incidence rate of persistent pain was 14.3 and 1.2% at the 3- and 6-month

Table 4. Adjusted Risks and Odds Ratios of Preoperative Variables to Predict Persistent Incisional Pain (n = 14,831)

	Frequency in Those with Persistent Pain, %	Absolute Risk Difference (95% CI), %	Adjusted Odds Ratio (95% CI)	*P* Values
Latin/Hispanic ethnicity	10 (2.0)	–1.4 (–1.6 to –1.2)	0.152 (0.08 to 0.289)	< 0.001
Native American/Australian ethnicity	6 (1.2)	–1.2 (–1.5 to –0.5)	0.303 (0.134 to 0.686)	0.004
South Asian ethnicity	34 (6.9)	–1.2 (–1.3 to –0.9)	0.315 (0.210 to 0.473)	< 0.001
Age, decades	—	–0.5 (–0.6 to –0.4)	0.71 (0.65 to 0.78)	< 0.001
History of tobacco use	239 (48.5)	0.4 (0 to 0.9)	1.23 (1.0 to 1.52)	0.048
Female sex	286 (57.8)	0.5 (0.1 to 1)	1.32 (1.08 to 1.61)	0.007
History of coronary artery disease	83 (16.8)	1.5 (0.7 to 2.4)	1.89 (1.44 to 2.47)	< 0.001
Surgery for fracture	36 (7.3)	1.8 (0.7 to 3.3)	2.08 (1.43 to 3.02)	< 0.001
History of chronic pain	109 (22.0)	2.1 (1.3 to 3)	2.29 (1.82 to 2.88)	< 0.001
Asian ethnicity	147 (29.7)	3.2 (2.2 to 4.4)	2.98 (2.36 to 3.76)	< 0.001
Body mass index	—	0 (–0.01 to 0.02)	1 (0.99 to 1.01)	0.730
Arabic/Persian ethnicity	2 (0.4)	–0.8 (–1.5 to 2)	0.54 (0.131 to 2.2)	0.386
African ethnicity	23 (4.6)	0.4 (–0.4 to 1.6)	1.22 (0.77 to 1.95)	0.400
Other ethnicity	2 (0.4)	–1.1 (–1.5 to 0.9)	0.37 (0.091 to 1.52)	0.169
History of diabetes	102 (20.6)	0 (–0.3 to 0.5)	1.01 (0.8 to 1.29)	0.905
Active cancer	60 (12.1)	–0.2 (–0.6 to 0.3)	0.87 (0.65 to 1.15)	0.325
History of peripheral vascular disease	32 (6.5)	0 (–0.6 to 0.9)	1.02 (0.66 to 1.56)	0.935

All variables were included in the final model. The reported estimates were adjusted to identify the independent effects of each variable.
*$P < 0.05$.

follow-up, respectively.[26] Given that the majority of studies on persistent postsurgical pain evaluate for pain within 6 months after surgery, with few assessing at follow-up dates 1 yr or later, this may also account for the lower incidence of pain found in our study. Third, VISION was restricted to surgical inpatients and therefore excluded outpatient surgeries that are typically associated with higher rates of persistent pain (*e.g.*, breast surgeries, inguinal hernia surgeries).

Missing data may have also contributed to a lower observed incidence rate. A total of 6,080 patients who were eligible to report on persistent pain were lost to follow-up at 1 yr (30% missing data). Our sensitivity analysis using multiple imputation suggests that the overall incidence may be slightly higher (3.7% *vs.* 3.3%) and that our observed incidence is likely an underestimation.

Our logistic regression models have confirmed previously identified risk factors for persistent pain after noncardiac surgery. Consistent with previous literature, younger age, females, and those with a history of chronic pain are at increased risk of persistent pain after surgery.[12,27–29] We also found that patients undergoing surgery for a fracture had double the risk for developing persistent pain, potentially because of neuronal injuries associated with trauma and the presence of preoperative pain, which is known to be associated with persistent pain.[30,31] Endoscopic surgeries were predictive of less persistent pain, and the mechanism for this may be due to potentially less tissue and neuronal injury compared to open surgeries.[30] A history of tobacco smoking was associated with persistent incisional pain, which is consistent with previous literature identifying tobacco use as a predictor of persistent pain after surgery.[32] However, similar to endoscopic surgeries, the association with tobacco smoking was not seen in our sensitivity analysis, indicating that these findings are not robust.

We also identified novel risk factors that may be associated with persistent pain. Ethnicity was one of the strongest predictors of persistent pain that we found. Specifically, Asian ethnicity was associated with the highest risk, whereas Latin/Hispanic, Native American/Australian, and South Asian ethnicities had the lowest risk for persistent pain. Racial and ethnic differences in pain thresholds are well documented in experimental pain studies, yet there are limited data on the clinical significance of these differences, particularly in the perioperative setting.[33–39] Furthermore, experimental studies are often conducted within the same geographic region (*i.e.*, all subjects come from the United States),[37] whereas in our sample, the patients were evaluated within their respective countries and continents, and thus any differences could also represent sociocultural variations.

Interestingly, history of coronary artery disease was associated with an increased risk of persistent pain. This is a novel finding, and the mechanism is not entirely clear. In addition, in the same model, peripheral vascular disease was not associated with persistent pain despite the strong overlap with coronary artery disease, suggesting a possible spurious finding or that a link exists that is specific to coronary atherosclerosis. Anti-inflammatory medications (NSAID or cyclooxygenase-2 inhibitors) taken regularly for the previous 7 days preoperatively but discontinued within 24 h of surgery were associated with an increased risk of persistent pain 1 yr later (compared to patients not taking NSAIDs or cyclooxygenase-2 inhibitors at all preoperatively). The mechanism for this is unclear, but it may indicate that patients were taking these medications daily for a pain disorder and that abrupt cessation of these medications led

Table 5. Adjusted Risks and Odds Ratios of Perioperative Variables to Predict Persistent Incisional Pain (n = 14,831)

	Frequency in Those with Persistent Pain, %	Absolute Risk Difference (95% CI), %	Adjusted Odds Ratio (95% CI)	*P* Values
Endoscopic surgery	91 (18.4)	–0.5 (–0.7 to –0.2)	0.71 (0.56 to 0.9)	0.005
NSAID 1 to 7 days preoperative, none less than 24 h preoperative	30 (6.1)	0.9 (0.1 to 2.1)	1.55 (1.05 to 2.3)	0.029
Postoperative PCA	207 (41.9)	1.5 (0.9 to 2.2)	1.92 (1.57 to 2.34)	< 0.001
Postoperative continuous nerve block	13 (2.6)	2.1 (0.4 to 5.1)	2.27 (1.21 to 4.24)	0.010
Cyclooxygenase-2 1 to 7 days preoperative, none less than 24 h preoperative	24 (4.8)	2.6 (1.1 to 4.9)	2.59 (1.66 to 4.07)	< 0.001
Insulin less than 24 h preoperative, none 1 to 7 days preoperative	25 (5.1)	3.3 (1.4 to 6.3)	3.02 (1.82 to 5.00)	< 0.001
Intraoperative nitrous oxide	33 (6.7)	–0.5 (–0.9 to 0.1)	0.72 (0.49 to 1.03)	0.075
Intraoperative spinal anesthesia	129 (26.1)	–0.2 (–0.5 to 0.2)	0.9 (0.72 to 1.13)	0.379
Intraoperative regional anesthesia	41 (8.3)	0.1 (–0.5 to 0.8)	1.03 (0.72 to 1.49)	0.854
Intraoperative epidural anesthesia	57 (11.5)	–0.5 (–0.9 to 0.2)	0.73 (0.48 to 1.1)	0.132
Postoperative epidural opioid analgesia	41 (8.3)	0.4 (–0.6 to 2.1)	1.21 (0.64 to 2.29)	0.553
Postoperative epidural local analgesia	43 (8.7)	0.9 (–0.3 to 3)	1.55 (0.83 to 2.87)	0.167
Postoperative IM/IV opioids	226 (45.8)	0.1 (–0.2 to 0.4)	1.04 (0.86 to 1.26)	0.666
Insulin 1 to 7 days preoperative, none less than 24 h preoperative	4 (0.8)	–0.8 (–1.4 to 0.7)	0.51 (0.188 to 1.41)	0.195
Insulin less than 24 h preoperative and 1 to 7 days preoperative	23 (4.6)	0 (–0.6 to 0.9)	0.99 (0.63 to 1.54)	0.963
Aspirin less than 24 h preoperative, none 1 to 7 days preoperative	2 (0.4)	2.7 (–0.7 to 14.7)	2.63 (0.61 to 11.38)	0.195
Aspirin 1 to 7 days preoperative, none less than 24 h preoperative	46 (9.3)	–0.1 (–0.6 to 0.4)	0.92 (0.67 to 1.27)	0.616
Aspirin less than 24 h preoperative and 1 to 7 days preoperative	25 (5.1)	0 (–0.6 to 0.9)	1 (0.66 to 1.53)	0.992
Oral hypoglycemia agent less than 24 h preoperative, none 1 to 7 days preoperative	—	–1.7 (–1.7 to –1.7)	0 (0 to 0)	0.998
Oral hypoglycemia agent 1 to 7 days preoperative, none less than 24 h preoperative	52 (10.5)	0.4 (–0.2 to 1.3)	1.25 (0.87 to 1.8)	0.218
Oral hypoglycemia agent less than 24 h preoperative and 1 to 7 days preoperative	21 (4.2)	–0.6 (–1 to 0)	0.63 (0.388 to 1.01)	0.054
Cyclooxygenase-2 less than 24 h preoperative, none 1 to 7 days preoperative	2 (0.4)	–0.7 (–1.5 to 2.3)	0.59 (0.143 to 2.43)	0.466
Cyclooxygenase-2 less than 24 h preoperative and 1 to 7 days preoperative	7 (1.4)	0.4 (–0.8 to 2.9)	1.23 (0.54 to 2.82)	0.625
NSAID less than 24 h preoperative, none 1 to 7 days preoperative	27 (5.5)	0.2 (–0.5 to 1.2)	1.09 (0.69 to 1.73)	0.712
NSAID less than 24 h preoperative and 1 to 7 days preoperative	14 (2.8)	–0.6 (–1.1 to 0.2)	0.65 (0.38 to 1.11)	0.116

All variables were included in the final model. The reported estimates were adjusted to identify the independent effects of each variable.

*$P < 0.05$.

IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia.

to increased perioperative pain.[40] Nevertheless, it raises questions about whether anti-inflammatory drugs should be discontinued before surgery in the setting where there are no identifiable contraindications. Furthermore, our model identified that insulin given within 24 h before surgery was associated with an increased risk of persistent pain. Although potentially spurious, there is evidence to suggest that abrupt improvements in glycemic control in the context of chronic hyperglycemia are associated with an increase in neuropathic pain, referred to as insulin neuritis.[41]

Postoperative PCA or continuous nerve catheter infusions appeared to be associated with a significant increase in persistent pain. Most likely, this finding results from confounding. The decision to offer a patient a PCA pump or nerve catheter after surgery is highly influenced by the intensity of their acute pain, and there is ample data to support that acute pain is associated with the development of chronic pain.[42,43] Because we did not collect acute postoperative pain scores, they were not adjusted for in the model, potentially confounding the relationship between PCA/nerve blocks and persistent incisional pain.

There are several limitations to this study. This study utilized the infrastructure of a large multicenter observational study, and for this reason, we were limited in collecting other baseline and perioperative variables that could be associated with persistent pain (*e.g.*, baseline pain catastrophizing, anxiety, depression, acute postoperative pain scores, persistent opioid use). The lack of pain-specific data available for statistical adjustments could have led to potential confounding in our analysis, as seen with our findings of PCA and continuous nerve blocks with persistent pain. Similarly, we were limited to the main study's follow-up periods (1 yr), preventing collection of pain scores at earlier time points that could inform a pain trajectory analysis.[44] Furthermore, although our outcome assessment included many of the criteria in the recently established International Association for the Study of Pain definition of chronic postsurgical pain (outcome assessment more than 3 months after surgery, not caused by preexisting pain and not caused by other reason [infection, malignancy]),[2] outcome assessment was limited to pain localized to the surgical incision (we did not assess for referred/projected pain to a nerve innervation territory or to a dermatome), and assessment occurred over a telephone follow-up. Given this slight variation in definitions and lack of validity testing, this could be a source of measurement error and bias (over- or underestimating actual incidences). Additionally, although our study included a large sample with multicenter data, it is important to recognize that our estimates are primarily generalizable to adult patients 45 yr old or older (VISION inclusion was limited

to this age group) undergoing inpatient surgical procedures (VISION did not include ambulatory surgeries, many of which are associated with high incidences of chronic post-surgical pain [*e.g.*, breast, inguinal hernia surgeries]).

In conclusion, our findings across a large international cohort of patients suggest that persistent pain is unfortunately a common and problematic complication after surgery. The majority of patients who develop persistent pain will report interference across aspects of daily life, and more than half will seek analgesic use, which can result in increased medication side effects and personal healthcare expenditures. Several demographic and perioperative factors have been identified to be associated with increased risk of persistent pain, and these data can help inform future studies in identifying high-risk patients and randomized trials on whether modification of these risk factors can lead to reduced rates of persistent pain.

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Competing Interests

Drs. Devereaux and McGillion are part of a research group with a policy of not accepting honoraria or other payments from industry for their own personal financial gain. They do accept honoraria/payments from industry to support research endeavors and costs to participate in meetings. Based on study questions Dr. Devereaux has originated and grants he has written, he has received grants from Abbott Diagnostics (Abbott Park, Illinois), Boehringer Ingelheim (Ingelheim am Rhein, Germany), Siemens (Munich, Germany), Philips Healthcare (Amsterdam, The Netherlands), and Roche Diagnostics (Basel, Switzerland). Based on study questions Dr. McGillion has originated and grants he has written, he has received peer-reviewed grants from government funding agencies that include in-kind support from Philips Healthcare, QoC Health (Toronto, Ontario, Canada), xahive (Ottawa, Ontario, Canada), Cloud DX (Kitchener, Ontario, Canada), and ThoughtWire (Toronto, Ontario, Canada). The other authors declare no competing interests.

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Canada. james.khan@medportal.ca. Anesthesiology's articles are made freely accessible to all readers on www.anesthesiology.org, for personal use only, 6 months from the cover date of the issue.

References

1. Crombie IK, Davies HT, Macrae WA: Cut and thrust: Antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 1998; 76:167–71
2. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD; IASP Taskforce for the Classification of Chronic Pain: The IASP classification of chronic pain for ICD-11: Chronic postsurgical or posttraumatic pain. Pain 2019; 160:45–52
3. Richebé P, Capdevila X, Rivat C: Persistent postsurgical pain: Pathophysiology and preventative pharmacologic considerations. Anesthesiology 2018; 129:590–607
4. Penny KI, Purves AM, Smith BH, Chambers WA, Smith WC: Relationship between the chronic pain grade and measures of physical, social and psychological well-being. Pain 1999; 79:275–9
5. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K: The impact of chronic pain in the community. Fam Pract 2001; 18:292–9
6. Von Korff M, Dworkin F, Le Resche L: Graded chronic pain status: An epidemiologic. Pain 1990; 40:279–91
7. Gureje O, Von Korff M, Simon GE, Gater R: Persistent pain and well-being: A World Health Organization Study in primary care. JAMA 1998; 280:147–51
8. Bair MJ, Robinson RL, Katon W, Kroenke K: Depression and pain comorbidity: A literature review. Arch Intern Med 2003; 163:2433–45
9. Karp JF, Scott J, Houck P, Reynolds CF III, Kupfer DJ, Frank E: Pain predicts longer time to remission during treatment of recurrent depression. J Clin Psychiatry 2005; 66:591–7
10. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R: Lost productive time and cost due to common pain conditions in the US workforce. JAMA 2003; 290:2443–54
11. Pagé MG, Kudrina I, Zomahoun HTV, Croteau J, Ziegler D, Ngangue P, Martin E, Fortier M, Boisvert EE, Beaulieu P, Charbonneau C, Cogan J, Daoust R, Martel MO, Néron A, Richebé P, Clarke H: A systematic review of the relative frequency and risk factors for prolonged opioid prescription following surgery and trauma among adults. Ann Surg 2020; 271:845–54
12. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: Risk factors and prevention. Lancet 2006; 367:1618–25
13. Visser EJ: Chronic post-surgical pain: Epidemiology and clinical implications for acute pain management. Acute Pain 2006; 8:73–81
14. Devereaux P, Chan M, Alonso-Coello P, Walsh M, Berwanger O, Villar J, Al E: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. J Am Med Assoc 2012; 307:2295–304
15. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR: A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49:1373–9
16. Kline R: Data preparation and screening, Principles and Practice of Structural Equation Modeling. New York, Guilford Press, 1998
17. Steyerberg E: Overfitting and optimism, Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York, Springer, 2009
18. Hoofwijk DM, Fiddelers AA, Peters ML, Stessel B, Kessels AG, Joosten EA, Gramke HF, Marcus MA: Prevalence and predictive factors of chronic postsurgical pain and poor global recovery 1 year after outpatient surgery. Clin J Pain 2015; 31:1017–25
19. Sansone P, Pace MC, Passavanti MB, Pota V, Colella U, Aurilio C: Epidemiology and incidence of acute and chronic post-surgical pain. Ann Ital Chir 2015; 86:285–92
20. Schug SA, Bruce J: Risk stratification for the development of chronic postsurgical pain. Pain Rep 2017; 2:e627
21. Werner MU, Kongsgaard UE: I. Defining persistent post-surgical pain: Is an update required? Br J Anaesth 2014; 113:1–4
22. Khan JS, Ladha KS, Abdallah F, Clarke H: Treating persistent pain after breast cancer surgery. Drugs 2020; 80:23–31
23. Wang L, Cohen JC, Devasenapathy N, Hong BY, Kheyson S, Lu D, Oparin Y, Kennedy SA, Romerosa B, Arora N, Kwon HY, Jackson K, Prasad M, Jayasekera D, Li A, Guarna G, Natalwalla S, Couban RJ, Reid S, Khan JS, McGillion M, Busse JW: Prevalence and intensity of persistent post-surgical pain following breast cancer surgery: A systematic review and meta-analysis of observational studies. Br J Anaesth 2020; 125:346–57
24. Poobalan AS, Bruce J, King PM, Chambers WA, Krukowski ZH, Smith WC: Chronic pain and quality of life following open inguinal hernia repair. Br J Surg 2001; 88:1122–6
25. Hinrichs-Rocker A, Schulz K, Järvinen I, Lefering R, Simanski C, Neugebauer EA: Psychosocial predictors and correlates for chronic post-surgical pain (CPSP): A systematic review. Eur J Pain 2009; 13:719–30
26. Gerbershagen HJ, Ozgür E, Dagtekin O, Straub K, Hahn M, Heidenreich A, Sabatowski R, Petzke F: Preoperative pain as a risk factor for chronic post-surgical pain: Six month follow-up after radical prostatectomy. Eur J Pain 2009; 13:1054–61

27. Gärtner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H: Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009; 302:1985–92
28. Maguire MF, Ravenscroft A, Beggs D, Duffy JP: A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006; 29:800–5
29. Massaron S, Bona S, Fumagalli U, Battafarano F, Elmore U, Rosati R: Analysis of post-surgical pain after inguinal hernia repair: A prospective study of 1,440 operations. Hernia 2007; 11:517–25
30. Wildgaard K, Ravn J, Kehlet H: Chronic post-thoracotomy pain: A critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg 2009; 36:170–80
31. Althaus A, Hinrichs-Rocker A, Chapman R, Arránz Becker O, Lefering R, Simanski C, Weber F, Moser KH, Joppich R, Trojan S, Gutzeit N, Neugebauer E: Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain 2012; 16:901–10
32. Khan JS, Devereaux PJ, LeManach Y, Busse JW: Patient coping and expectations about recovery predict the development of chronic post-surgical pain after traumatic tibial fracture repair. Br J Anaesth 2016; 117:365–70
33. Chan MYP, Hamamura T, Janschewitz K: Ethnic differences in physical pain sensitivity: Role of acculturation. Pain 2013; 154:119–23
34. Lu Q, Zeltzer L, Tsao J: Multiethnic differences in responses to laboratory pain stimuli among children. Health Psychol 2013; 32:905–14
35. Ahn H, Weaver M, Lyon DE, Kim J, Choi E, Staud R, Fillingim RB: Differences in clinical pain and experimental pain sensitivity between Asian Americans and whites with knee osteoarthritis. Clin J Pain 2017; 33:174–80
36. Hsieh AY, Tripp DA, Ji LJ, Sullivan MJ: Comparisons of catastrophizing, pain attitudes, and cold-pressor pain experience between Chinese and European Canadian young adults. J Pain 2010; 11:1187–94
37. Rahim-Williams B, Riley JL III, Williams AK, Fillingim RB: A quantitative review of ethnic group differences in experimental pain response: Do biology, psychology, and culture matter? Pain Med 2012; 13:522–40
38. Watson PJ, Latif RK, Rowbotham DJ: Ethnic differences in thermal pain responses: A comparison of South Asian and white British healthy males. Pain 2005; 118:194–200
39. Al-Hashimi M, Scott S, Griffin-Teall N, Thompson J: Influence of ethnicity on the perception and treatment of early post-operative pain. Br J Pain 2015; 9:167–72
40. Katz J, Jackson M, Kavanagh BP, Sandler AN: Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996; 12:50–5
41. Gibbons CH, Freeman R: Treatment-induced neuropathy of diabetes: An acute, iatrogenic complication of diabetes. Brain 2015; 138:43–52
42. Chapman CR, Vierck CJ: The transition of acute postoperative pain to chronic pain: An integrative overview of research on mechanisms. J Pain 2017; 18:359.e1–38
43. Gilron I, Vandenkerkhof E, Katz J, Kehlet H, Carley M: Evaluating the association between acute and chronic pain after surgery: Impact of pain measurement methods. Clin J Pain 2017; 33:588–94
44. Pagé MG, Katz J, Romero Escobar EM, Lutzky-Cohen N, Curtis K, Fuss S, Clarke HA: Distinguishing problematic from nonproblematic postsurgical pain: A pain trajectory analysis after total knee arthroplasty. Pain 2015; 156:460–8

Appendix

Table A1. Patient Characteristics of Those with Mild, Moderate, and Severe Pain in Those with Persistent Incisional Pain

Variables	Mild Pain (Pain Scores 0 to 3; n = 251)	Moderate Pain (Pain Scores 4 to 6; n = 170)	Severe Pain (Pain Scores 7 to 10; n = 66)
Mean age, yr (SD)	68.0 (10.6)	64.7 (9.9)	64.8 (8.4)
Female sex, no. (%)	144 (50.5)	102 (60.0)	36 (54.5)
Mean body mass index, kg/m^2 (SD)	27.8 (6.9)	28.6 (7.0)	29.7 (6.7)
Diabetes, no. (%)	58 (23.1)	30 (17.6)	13 (19.7)
Active cancer, no. (%)	42 (16.7)	12 (7.1)	4 (6.1)
History of tobacco use, no. (%)	108 (43.4)	87 (51.2)	41 (62.1)
Coronary artery disease, no. (%)	44 (17.7)	25 (14.7)	11 (16.7)
Peripheral vascular disease, no. (%)	13 (5.2)	14 (8.2)	4 (6.1)
History of chronic pain, no. (%)	48 (19.1)	41 (24.1)	19 (28.8)

Pain scores indicate the patient rating of pain on a numeric rating scale from 0 to 10.

Table A2. Neuropathic Pain Characteristics in Those with Persistent Incisional Pain

Pain Characteristic	Number Reporting Pain, no. (%)	Score 0 to 10, Mean (SD)
Increased pain to touch	284 (57.4)	2.7 (3.1)
Numbness	233 (47.1)	2.1 (2.9)
Tingling	193 (39.6)	1.8 (2.8)

Table A3. Impact of Medications Taken for Persistent Incisional Pain on Aspects of Daily Living

Aspect of Daily Life	Medications for Incisional Pain	Scale 0 to 10, Mean (SD)
General activity	Yes	4.7 (3.3)*
	No	2.0 (2.7)
Mood	Yes	4.0 (3.3)*
	No	1.7 (2.4)
Walking activity	Yes	4.6 (3.4)*
	No	2.2 (2.8)
Normal work	Yes	4.8 (3.7)*
	No	2.0 (2.8)
Relations	Yes	2.7 (3.3)*
	No	1.0 (2.0)
Sleep	Yes	4.1 (3.3)*
	No	1.9 (2.8)
Enjoyment of life	Yes	3.9 (3.4)*
	No	1.6 (2.4)

*$P < 0.001$.

Table A4. Adjusted Risks Odds Ratios of Perioperative Variables to Predict Persistent Incisional Pain

	Frequency of Those with Persistent Pain, %	Absolute Risk Difference (95% CI)	Adjusted Odds Ratio (95% CI)	*P* Values
Active cancer	60 (12.1)	–0.1 (–0.5 to 0.5)	0.97 (0.72 to 1.32)	0.868
African ethnicity	23 (4.6)	0.5 (–0.3 to 1.8)	1.29 (0.8 to 2.08)	0.297
Age, decades		–0.6 (–0.7 to –0.5)	0.66 (0.6 to 0.73)	< 0.001
Arabic/Persian ethnicity	2 (0.4)	–0.6 (–1.4 to 2.6)	0.63 (0.15 to 2.62)	0.530
Aspirin less than 24 h preoperative and 1 to 7 days preoperative	25 (5.1)	–0.3 (–0.8 to 0.5)	0.81 (0.5 to 1.32)	0.399
Aspirin less than 24 h preoperative, none 1 to 7 days preoperative	2 (0.4)	2.5 (–0.9 to 17.1)	2.51 (0.47 to 13.35)	0.280
Aspirin 1 to 7 days preoperative, none less than 24 h preoperative	46 (9.3)	–0.1 (–0.6 to 0.6)	0.95 (0.67 to 1.36)	0.799
Asian ethnicity	147 (29.7)	4.6 (3.2 to 6.3)	3.88 (2.98 to 5.06)	< 0.001
Body mass index		0 (–0.02 to 0.02)	1 (0.99 to 1.01)	0.989
Cyclooxygenase-2 less than 24 h preoperative and 1 to 7 days preoperative	7 (1.4)	0.1 (–0.9 to 2.4)	1.05 (0.45 to 2.49)	0.907
Cyclooxygenase-2 less than 24 h preoperative, none 1 to 7 days preoperative	2 (0.4)	–0.8 (–1.5 to 2)	0.53 (0.13 to 2.22)	0.385
Cyclooxygenase-2 1 to 7 days preoperative, none less than 24 h preoperative	24 (4.8)	1.8 (0.5 to 3.9)	2.12 (1.32 to 3.41)	0.002
Oral hypoglycemia agent less than 24 h preoperative and 1 to 7 days preoperative	21 (4.2)	–0.4 (–1 to 0.7)	0.76 (0.41 to 1.4)	0.378
Oral hypoglycemia agent less than 24 h preoperative, none 1 to 7 days preoperative	0 (0)	0 (0 to 0)	0 (0 to 0)	0.998
Oral hypoglycemia agent 1 to 7 days preoperative, none less than 24 h preoperative	52 (10.5)	0.2 (–0.5 to 1.5)	1.14 (0.68 to 1.91)	0.618
Postoperative epidural local analgesia	43 (8.7)	0.4 (–0.6 to 2.4)	1.27 (0.66 to 2.47)	0.475
Endoscopic surgery	91 (18.4)	–0.4 (–0.7 to 0.1)	0.78 (0.59 to 1.03)	0.076
Otolaryngologic surgeries	7 (1.4)	0.7 (–0.7 to 4.1)	1.45 (0.59 to 3.57)	0.424
Postoperative epidural opioid analgesia	41 (8.3)	–0.1 (–0.9 to 1.5)	0.95 (0.47 to 1.9)	0.886
Intraoperative epidural anesthesia	57 (11.5)	0.6 (–0.3 to 2)	1.39 (0.85 to 2.25)	0.185
Female sex	286 (57.8)	0.4 (0.1 to 0.9)	1.27 (1.04 to 1.57)	0.022
General surgery	97 (19.6)	0.4 (–0.4 to 1.9)	1.27 (0.76 to 2.14)	0.360
History of coronary artery disease	83 (16.8)	1.6 (0.8 to 2.7)	1.99 (1.48 to 2.68)	< 0.001
History of chronic pain	109 (22.0	1.4 (0.7 to 2.2)	1.83 (1.43 to 2.34)	< 0.001
History of diabetes	102 (20.6)	–0.1 (–0.7 to 0.8)	0.96 (0.61 to 1.51)	0.862
History of peripheral vascular disease	32 (6.5)	0.3 (–0.5 to 1.7)	1.21 (0.73 to 2.01)	0.450
History of tobacco use	239 (48.3)	0.4 (0 to 0.9)	1.23 (0.99 to 1.52)	0.058
Postoperative IM/IV opioids	226 (45.7)	0.2 (–0.1 to 0.6)	1.13 (0.92 to 1.39)	0.241
Insulin less than 24 h preoperative and 1 to 7 days preoperative	23 (4.6)	0 (–0.7 to 1.2)	0.99 (0.58 to 1.7)	0.980
Insulin less than 24 h preoperative, none 1 to 7 days preoperative	25 (5.1)	1.5 (0.1 to 3.8)	1.89 (1.05 to 3.39)	0.033
Insulin 1 to 7 days preoperative, none less than 24 h preoperative	4 (0.8)	–0.9 (–1.5 to 0.8)	0.44 (0.13 to 1.47)	0.183
Latin/Hispanic ethnicity	10 (2.0)	–1.3 (–1.5 to –1)	0.21 (0.11 to 0.41)	< 0.001
Low-risk surgeries	152 (30.7)	0.2 (–0.5 to 1.4)	1.11 (0.68 to 1.83)	0.679
Native American/Australian ethnicity	6 (1.2)	–1 (–1.4 to 0)	0.43 (0.19 to 0.98)	0.046
Intraoperative regional anesthesia	41 (8.3)	–0.1 (–0.6 to 0.7)	0.95 (0.64 to 1.41)	0.788
Postoperative continuous nerve block	13 (2.6)	1.1 (–0.2 to 3.6)	1.67 (0.86 to 3.22)	0.127
Neurosurgeries	47 (9.5)	1.1 (–0.2 to 3.2)	1.64 (0.9 to 3)	0.109
Intraoperative nitrous oxide	33 (6.7)	0.3 (–0.4 to 1.3)	1.19 (0.79 to 1.8)	0.396
NSAID less than 24 h preoperative and 1 to 7 days preoperative	14 (2.8)	–0.4 (–1 to 0.5)	0.74 (0.42 to 1.29)	0.290
NSAID less than 24 h preoperative, none 1 to 7 days preoperative	25 (5.5)	0.5 (–0.4 to 1.8)	1.28 (0.79 to 2.08)	0.320
NSAID 1 to 7 days preoperative, none less than 24 h preoperative	30 (6.1)	1 (0.1 to 2.4)	1.63 (1.07 to 2.47)	0.023
Orthopedic surgeries	143 (28.9)	0.9 (–0.2 to 2.9)	1.56 (0.88 to 2.77)	0.127
Other ethnicity	2 (0.4)	–0.9 (–1.5 to 1.6)	0.48 (0.12 to 1.98)	0.312
Postoperative PCA	207 (41.8)	0.9 (0.4 to 1.6)	1.55 (1.23 to 1.96)	< 0.001
South Asian ethnicity	34 (6.9)	–1 (–1.3 to –0.6)	0.39 (0.25 to 0.63)	< 0.001
Intraoperative spinal anesthesia	129 (26.1)	0.1 (–0.3 to 0.8)	1.08 (0.8 to 1.46)	0.622
Surgery for fracture	36 (7.3)	1.6 (0.6 to 3.2)	1.99 (1.34 to 2.96)	0.001
Thoracic surgery	14 (2.8)	1.2 (–0.3 to 4.3)	1.75 (0.83 to 3.69)	0.138
Urologic–gynecologic surgeries	36 (7.3)	–0.7 (–1.1 to 0)	0.61 (0.37 to 1.01)	0.052
Vascular surgery	18 (3.6)	–0.1 (–0.9 to 1.7)	0.96 (0.45 to 2.06)	0.914

IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia.