

Prediction of postoperative pain using path analysis in older patients

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Abstract

Purpose Effective postoperative pain management is important for older surgical patients because pain affects perioperative outcomes. A prospective cohort study was conducted to describe the direct and indirect effects of patient risk factors and pain treatment in explaining levels of postoperative pain in older surgical patients.

Methods We studied patients who were 65 years of age or older and were scheduled for major noncardiac surgery with a postoperative hospital stay of at least 2 days. The numeric rating scale (0 = no pain, 10 = worst possible pain) was used to measure pain levels before surgery and once daily for 2 days after surgery. Path analysis was performed to examine the association between predictive variables and postoperative pain levels.

Results Three hundred fifty patients were studied. We found that preoperative pain level, use of preoperative opioids, female gender, higher ASA physical status, and postoperative pain control methods were the strongest

predictors of postoperative pain as measured on the first day after surgery. Younger age, greater preoperative symptoms of depression, and lower cognitive function also contributed to higher postoperative pain levels. Pain levels on the second day after surgery were strongly predicted by preoperative pain level, use of preoperative opioids, surgical risk, and pain and opioid dose on postoperative day 1. However, younger age, female gender, higher ASA physical status, greater preoperative symptoms of depression, lower cognitive function, and postoperative pain control methods indirectly contributed to pain levels on the second day after surgery.

Conclusion Although preoperative pain and use of preoperative opioids have the strongest effects on postoperative pain, clinicians should be aware that other factors such as age, gender, surgical risk, preoperative cognitive impairment, and depression also contribute to reported postoperative pain. Based on significant statistical correlations, these study results can contribute to more effective postoperative care for those patients having the risk factors studied here. Preoperative treatment/intervention based in part on factors such as preoperative pain, use of preoperative opioids, and depression may improve postoperative pain management.

Keywords Aged · 80 and over · Aging · Pain · Postoperative

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Introduction

Since 1999, when the Joint Commission on Accreditation of Healthcare Organizations set the standards for the appropriate assessment and management of pain, pain has

been recognized as the fifth vital sign in the United States [1]. Appropriate assessment and management of pain is an important component of perioperative care for older surgical patients, because appropriate pain control may contribute to better postoperative outcomes [2, 3]. In contrast, inadequate pain control may increase sympathetic nervous system tone and contribute to cardiovascular complications such as myocardial ischemia or dysrhythmias [4]. Poorly managed pain may also lead to inadequate respiration and subsequent atelectasis or pneumonia [4]. In addition, in older patients, postoperative pain management is an important factor related to delirium [5]. Furthermore, inadequate pain control in the acute postoperative period may result in chronic post-surgical pain [6, 7].

In many previous studies, elderly patients have been excluded from clinical studies, so that factors that affect postoperative pain in older patients are not well understood. Identifying which predictors are associated with postoperative pain perception may enable the management of older patients in a more evidence-based fashion.

The aims of the present study were to identify predictors of postoperative pain levels in older surgical patients that we hypothesize will be affected by preoperative factors [age, gender, American Society of Anesthesiologists physical status classification (ASA PS), preoperative pain levels, preoperative use of opioids, depressive symptoms, and baseline cognitive status], intraoperative factors (surgical risk [8], which includes type of surgery, length of surgery, and blood loss), and postoperative factors (postoperative pain control methods) (Fig. 1). These factors were selected based on results from previous studies [9–12], and also based on a plausible biological link between possible predictors and postoperative pain. The primary outcomes in this study are pain levels on postoperative days one (POD1) and day two (POD2), as reported by patient using the numerical rating scale (NRS).

Methods

Patient recruitment

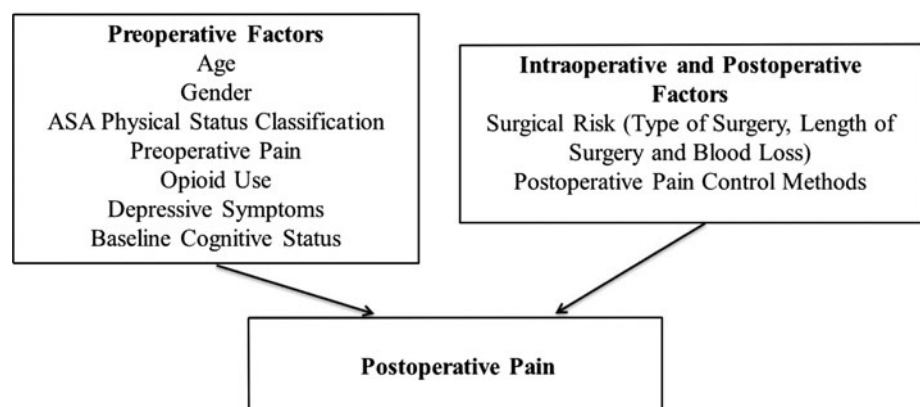
The study was approved by the Institutional Review Board of the University of California, San Francisco, and was part of a larger study examining the pathophysiology of postoperative cognitive changes conducted from 2001 to 2006 at the University of California, San Francisco Medical Center.

To be included in the study, patients had to be at least 65 years of age and have undergone elective noncardiac surgery requiring a postoperative stay of at least 2 days. They also had to speak English and to be able to provide written informed consent. The attending physicians determined the type of anesthesia given and the method of postoperative pain management used. No aspect of clinical care was modified specifically for this study. Patients who received intravenous patient-controlled analgesia (IV-PCA) or oral pain medications postoperatively were included in the study. We excluded patients who received postoperative neuraxial analgesia or peripheral nerve blocks for postoperative analgesia to minimize confounding effects of additional postoperative pain management methods. Data for a subset of patients in this study ($n = 331$) were included in a previous paper evaluating the effect of pain and pain management on postoperative cognition [5].

Preoperative assessment

The preoperative interview was conducted by a trained research assistant in the preoperative anesthesia clinic, typically less than 2 weeks before surgery. The patient's health information and the potential covariates associated with postoperative pain, including age, ASA PS, preoperative pain levels, preoperative depressive symptoms, and use of preoperative opioids, were obtained.

Fig. 1 Conceptual framework for prospective cohort study of possible predictors of postoperative pain. ASA American Society of Anesthesiologists



Patients were asked to rate their pain levels at rest using the 11-point numeric rating scales (NRS) from “no pain” to “worst possible pain” [13]. Preoperative symptoms of depression were measured using the 15-item Geriatric Depression Scale (GDS) [14]. The GDS was selected because it is a valid depression screen that is easy to administer in the preoperative period [15]. The score on the GDS reflects the total number of depressive symptoms reported by the patient. Baseline cognitive status was assessed in person or over the phone preoperatively using the Telephone Interview for Cognitive Status (TICS) [16]. TICS is an 11-item test (maximum, 41 points) that correlates well with the Mini-Mental State Examination and is widely used for screening of dementia. Scores below 30 on the TICS are considered to be cognitively impaired [17].

Intraoperative data

Data including type of surgery, length of surgery, and intraoperative blood loss were measured. Surgical risk was determined for each patient based on collected data and divided into three levels (low, intermediate, and high) [8]. Definition of surgical risk levels is noted in Appendix 1.

Postoperative assessment of pain and pain management

Postoperative interviews were performed once a day for the first 2 postoperative days. The same trained research assistant conducted the interviews, which occurred between approximately 9 a.m. and 12 p.m., in the patient’s hospital room. Pain levels at rest were measured in the same way as the preoperative evaluation, using the NRS. Information about postoperative pain management (use of IV-PCA or oral opioids) was obtained through review of medical records. Hydromorphone is the standard opioid used in our institution for IV-PCA administration. The typical IV-PCA was set to deliver a 0.2-mg intravenous bolus of hydromorphone per demand, with lockout time of 6 min without continuous background infusion. Dosages for PCA administration were not modified based on age. If hydromorphone was not used (for example, because of patient allergy or sensitivity), morphine sulfate or fentanyl was used. Morphine sulfate and fentanyl doses were converted to hydromorphone using the conversion formula: 5 mg morphine sulfate = 1 mg hydromorphone, 50 μ g fentanyl = 1 mg hydromorphone. Oral pain medication [e.g., hydrocodone with acetaminophen (5 mg/500 mg)] was given every 4–6 h as needed.

Statistical analysis

Path analysis was performed to examine the relationships among postoperative pain, use of postoperative opioids, and

multiple variables (age, ASA PS, preoperative antidepressants, preoperative GDS scores, preoperative TICS, preoperative pain levels, surgical risk, and postoperative pain control methods). Path analysis is an extension of multiple regression that can provide estimates of the magnitude and significance of hypothesized causal connections between sets of variables [18]. In path analysis, hypotheses about relationships among variables are often depicted in a path diagram. Figure 2 represents a path diagram to investigate our hypothesis. In contrast to multiple regression analysis, path modeling allows assessment of the direct and indirect effects of predictors on the dependent variables. Also, in contrast to multiple regression analysis, which involves the computation of one model for each dependent variable, path modeling can be used to analyze multiple dependent variables simultaneously and provides an overall test of model fit. Preoperative GDS scores and opioid dose on POD1 and POD2 were not normally distributed. Therefore, to reduce variation and also to satisfy the assumption of multivariate normality, they were transformed by $\log(x + 0.0001)$. If 70% of the items of TICS and GDS were present, missing imputation with itemized mean was applied. Standardized regression weights (path coefficients) were reported on each arrow. The significance of a path coefficient was tested by using the *t* test, which evaluates if the coefficient is significantly different than zero. A value of zero for a coefficient would indicate no association. When a variable has an arrow directed toward a dependent variable, it is said to have a direct effect. When a variable has an effect on the dependent variable through another variable, it is said to have an indirect effect.

We evaluated the goodness of fit of the hypothesized model shown in Fig. 2. The χ^2 value, corresponding *P* value, goodness-of-fit test index (GFI), the root mean square error of approximation (RMSEA), standardized root mean squared residual (SRMR), non-normed fit index (NNFI), and comparative fit index (CFI) were taken as indicators for the overall goodness of fit of the model. Nonsignificant χ^2 , values of the RMSEA less than 0.06, and values of the SRMR less than 0.08 are considered to indicate a very good fit. The GFI, NNFI, and CFI should be 0.90 or higher for a good fit [18]. According to these indices, the overall model fit of the path model was satisfactory [$\chi^2(46, n = 350) = 60.325, P = 0.051$; SRMR = 0.045; RMSEA = 0.033; GFI = 0.986; NNFI = 0.954; CFI = 0.970]. All analyses were performed in SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

We studied 350 patients. The mean age was 73.4 ± 6.2 years (range, 65–96 years): 33.4% of patients

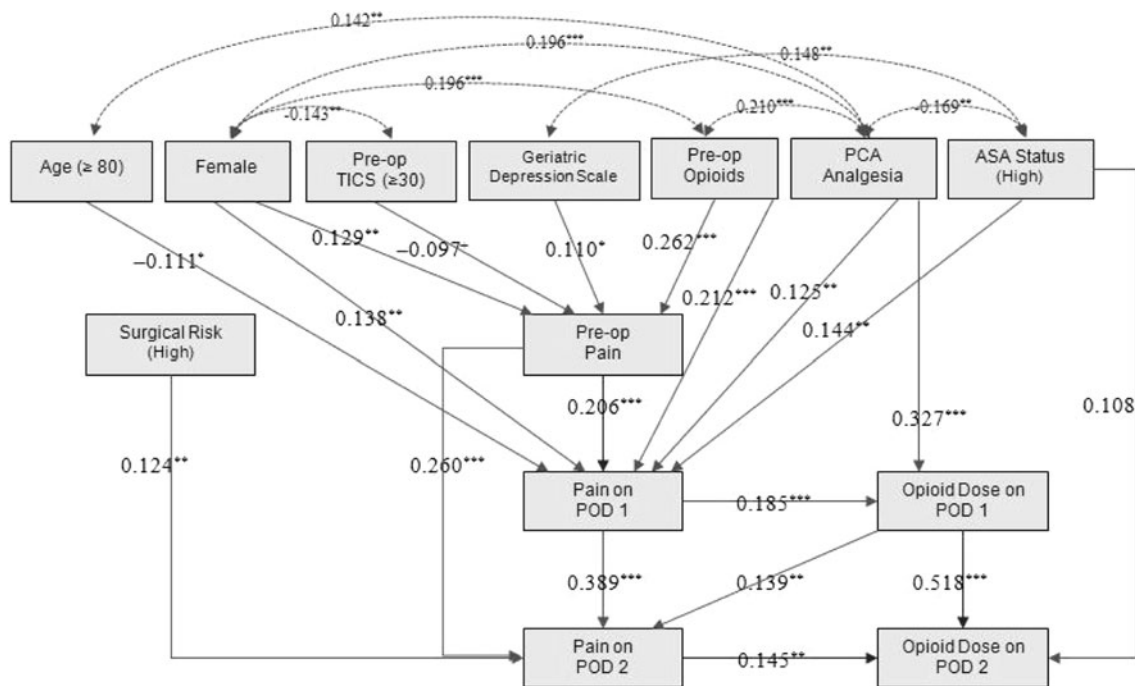


Fig. 2 Postulated path model for postoperative pain. Association between multiple variables and postoperative pain is shown by arrows extending from each variables to pain on POD1 and POD2. Numbers

on each arrow are standardized path coefficients. The higher the coefficients indicate the stronger the association

were 65–69 years old, 49.4% were 70–79 years old, and 17.2% were 80 years old or older. The incidence of pre-operative opioid use was 31.7%. Mean preoperative pain levels, postoperative pain levels, postoperative intravenous opioid usage, and additional clinical data are listed on Table 1.

Path analysis

As shown in Fig. 2 and Appendix 2, use of preoperative opioids (0.262 ; $P < 0.001$), female gender (0.129 ; $P < 0.05$), and greater number of preoperative depressive symptoms (GDS) (0.110 ; $P < 0.05$) were associated with greater preoperative pain. Higher cognitive function (TICS ≥ 30) was associated with less preoperative pain (-0.097 ; $P = 0.054$). The seven dotted lines in Fig. 2 were included to show the expected associations between the exogenous variables. For example, female gender was associated with lower cognitive functioning (-0.143 ; $P < 0.01$), use of preoperative opioids (0.196 ; $P < 0.001$), and use of IV-PCA (0.196 ; $P < 0.001$). Higher ASA PS was negatively associated with use of IV-PCA (-0.169 ; $P < 0.01$) but positively associated with more preoperative depressive symptoms (0.148 ; $P < 0.01$) and age ≥ 80 (0.142 ; $P < 0.01$). Use of pre-operative opioids was positively associated with use of IV-PCA (0.210 ; $P < 0.001$).

Predictors of postoperative pain on POD1

Six predictors were identified (Fig. 2). Use of preoperative opioids (0.212 ; $P < 0.001$), higher ASA PS (0.144 ; $P < 0.01$), greater preoperative pain (0.206 ; $P < 0.001$), female gender (0.138 ; $P < 0.01$), and use of IV-PCA (0.125 ; $P < 0.01$) were associated with higher postoperative pain levels on POD1. Different from other predictors, age 80 years or older (-0.111 ; $P < 0.05$) was negatively associated with postoperative pain, which indicates that patients 80 years or older reported lower level of postoperative pain on POD1. Intraoperative factors (surgical risk, which includes type of surgery, length of surgery, and blood loss) were not found to be a significant predictor. Pain on POD1 was also indirectly affected by preoperative psychological state, with higher cognitive functioning contributing to lower pain levels and higher number of depressive symptoms contributing to higher POD1 pain levels (Appendix 2).

Predictors of postoperative pain on POD2

Preoperative pain (0.260 ; $P < 0.001$), pain level (0.389 ; $P < 0.001$), and opioid dose (0.139 ; $P < 0.01$) affected postoperative pain on POD1, and higher surgical risk (0.124 ; $P < 0.01$) affected postoperative pain on POD2. In addition, predictors for postoperative pain on POD1 also

Table 1 Demographics and perioperative data (*n* = 350)

Variables	Patients <i>n</i> (%) or mean ± SD
Age	
64–69 years	117 (33.4%)
70–79 years	173 (49.4%)
≥80 years	60 (17.1%)
Gender	
Female	172 (49.1%)
Male	178 (50.9%)
ASA PS	
1 and 2	176 (50.3%)
≥3	174 (49.7%)
Preoperative antidepressant	
No	292 (83.4%)
Yes	58 (16.6%)
Preoperative opioids	
No	239 (68.3%)
Yes	111 (31.7%)
Preoperative pain at rest (NRS)	2.2 ± 2.8
Geriatric Depression Scale (GDS)	2.9 ± 2.6
<6	298 (85.1%)
≥6	52 (14.9%)
TICS scores	32.4 ± 3.6
< 30	64 (18.3%)
≥ 30	286 (81.7%)
Type of surgery	
Ear–nose–throat	4 (1.1%)
General	22 (6.3%)
Gynecological	27 (7.7%)
Neurological	46 (13.1%)
Orthopedic	178 (50.9%)
Plastic	3 (0.9%)
Thoracic	14 (4.0%)
Urologic	36 (10.3%)
Vascular	20 (5.7%)
Intraoperative blood loss (ml)	738.1 ± 1363.5
Surgical risk	
Low	7 (2.0%)
Intermediate	278 (79.4%)
High	65 (18.6%)
Analgesia	
IV-PCA analgesia	261 (74.6%)
Oral analgesia	89 (25.4%)
Pain at rest on POD1 (NRS)	3.5 ± 2.8
Pain at rest on POD2 (NRS)	2.8 ± 2.8
Opioid dose on POD1	6.3 ± 9.5 (mg)*

Table 1 continued

Variables	Patients <i>n</i> (%) or mean ± SD
Opioid dose on POD2	3.0 ± 5.9 (mg)*

ASA PS American Society of Anesthesiologists Physical Status Classification, NRS numeric rating scale, IV-PCA intravenous patient-controlled analgesia, POD postoperative day, SD standard deviation, TICS telephone interview of cognitive status

*The results are shown as dosage of hydromorphone

indirectly affected postoperative pain on POD2 (younger age, female, higher ASA PS, greater number of preoperative depressive symptoms, lower cognitive functioning, and use of IV-PCA analgesia).

Postoperative opioid dose on POD1 and POD2

Figure 2 also shows that pain level on POD1 (0.185; *P* < 0.001) and use of IV-PCA analgesia (0.327; *P* < 0.001) were associated with opioid dose on POD1. All the predictors of postoperative pain except higher preoperative TICS had indirect effects on opioid dose on POD1. For example, use of preoperative opioids (0.049; *P* < 0.01), preoperative pain (0.038; *P* < 0.01), female (0.030; *P* < 0.01), and higher ASA PS (0.027; *P* < 0.05) had effects on opioid dose on POD1 through postoperative pain.

In addition to the variables associated with opioid dose on POD1, opioid dose on POD1 (0.518; *P* < 0.001), pain level on POD2 (0.145; *P* < 0.01), and higher ASA PS (0.108; *P* < 0.05) were associated with opioid dose on POD2.

Discussion

Clinicians have intuitively understood that pathways to postoperative pain are complex for reasons of the multiple causes of postoperative pain and the interrelationships among them. This study provides empirical evidence that many interrelated preoperative and postoperative patient factors both directly and indirectly affect self-reported postoperative pain levels and opioid use in older surgical patients. The results in the path model demonstrate how a patient’s physical and psychological statuses directly contribute to preoperative pain and both directly and indirectly contribute to postoperative pain. Further, the model elucidates how these patient-related factors combine to affect the postoperative dose of opioids. In contrast to traditional regression models, use of a path model allowed simultaneous modeling of both the direct and indirect predictors of

postoperative pain and opioid dose the first 2 days after elective surgery. For example, factors that have a direct association with pain on POD1 include age, preoperative pain levels, preoperative opioid use, ASA PS, and the type of postoperative pain management (IV-PCA). Factors that indirectly affected postoperative pain were the patient's preoperative physical and psychological statuses. The results of the model provide a basis for the development of a heuristic model of the causes of postoperative pain in older surgical patients.

Our study shows that preoperative pain is an important predictor of postoperative pain. This result is consistent with previous studies reporting that preoperative pain is a predictor of postoperative pain [9, 10, 19, 20]. A possible explanation is that preoperative pain could induce changes in pain processing, i.e., central sensitization or neuroplasticity [19, 20]. Wilder-Smith et al. [21] studied the sensory change (neuroplasticity) accompanying back surgery by measuring pain thresholds to transcutaneous electric stimulation. They concluded that preoperative back pain is associated with significant changes in central nervous nociceptive processing and induces diverse manifestation of central neuroplasticity, depending on the nature of the pain, its predominant site, and its chronicity. Our study also shows that ASA PS was associated with higher postoperative pain. A possible explanation is that patients with higher ASA PS are more likely to be chronically ill and have coexistent chronic pain. To our knowledge, only a few studies have examined the relationship between ASA PS and postoperative pain. Caumo et al. [9], who studied patients undergoing elective abdominal surgery, similarly reported that higher ASA PS was associated with increased postoperative pain. In contrast, Chung et al. [22] reported that, in an ambulatory surgery setting, ASA 1 patients had a higher incidence of severe pain than sicker patients, i.e., ASA 2 or 3 patients. However, this study did not measure pain beyond the day of surgery and did not separately evaluate the impact of preoperative burden of illness on older patients. It is not immediately apparent why surgical risk was associated with pain on POD2 only. Overall surgical risk includes type of surgery, length of surgery, and intraoperative blood loss. Therefore, it is a more comprehensive way to categorize the severity of surgery.

Similar to our results, the recent review by Ip et al. [23] suggests that older age is associated with less postoperative pain. The explanation as to why older age is associated with lower self-reported pain is not apparent. Previous research suggests that this age-related difference in pain might be caused by change in pain processing and pain modulation mechanisms [24]. However, definitive studies are lacking to determine whether older individuals under-report pain or truly have lower pain sensitivity.

In our study, postoperative IV-PCA usage was associated with higher postoperative pain levels when compared with use of oral analgesics. The need for IV-PCA versus oral analgesics is probably a surrogate marker for more intense postoperative pain, as oral analgesics are typically useful only for mild to moderate acute postoperative pain.

There are several potential limitations to this study. First, self-reported pain may not completely capture the whole spectrum of pain perception; however, the NRS is still the most commonly used pain assessment tool in the clinical setting. Second, we measured pain once daily for postoperative periods. Because acute postoperative pain is dynamic, we may not have captured the potential fluctuation of this parameter. However, from our experience, pain assessment once in the morning versus twice a day assessments showed no significant difference in pain scores. In a separate pilot study of 20 patients evaluating the potential differences in pain scores between assessments once a day versus twice a day, we found that only 2% of pain scores were significantly different between the two methods. Third, we did not include the measurement of other psychological and emotional factors (e.g., anxiety or fear) that may modulate pain [10, 25]. Fourth, we did not differentiate between acute nociceptive and chronic neuropathic pain. Fifth, generalizability of findings is limited to only patients who received IV-PCA opioids for postoperative management, which was done to minimize the potential bias of use of additional pain adjuvant techniques such as epidural or peripheral nerve blocks. Although the use of IV-PCA has been typically directed toward those with anticipated moderate to severe postoperative pain, the attending physicians' discretionary choice of postoperative pain management may have influenced the results of this study. In addition, the results shown here may not be directly applicable to patients who had relatively minor surgeries.

Despite these limitations, the study provides a novel method for understanding the strength of both direct and indirect contributors to postoperative pain and opioid dose. For example, both pain on POD2 and surgical risk were strong predictors of opioid dose on POD2. However, there were multiple pathways to pain on POD2, including both the direct effects of prior pain and the indirect effects of age and opioid dose on the prior day. These multiple pathways to POD2 pain contributed to opioid dose on POD2. These results suggest that opioid dosing is caused by to a complex set of prior, current, direct, and indirect factors. The findings of this study may provide a better understanding of additional factors that affect acute postoperative pain, opioid dose, and pain management.

Because postoperative pain control is critical to surgical outcomes, anticipating which patients may be more likely

to report severe postoperative pain is important. Our study shows that there are many direct and indirect factors associated with postoperative pain.

In summary, in a group of older patients undergoing major noncardiac surgery, preoperative pain, use of preoperative opioids, age, ASA PS and postoperative pain control methods (use of IV-PCA) were the most important predictors of postoperative pain. However, gender and patients' preoperative psychological status also directly contributed to preoperative pain and indirectly contributed to postoperative pain. Further investigation is necessary to determine whether intensifying preoperative pain management and associated factors with preoperative pain (e.g., depression) may decrease acute postoperative pain.

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Conflict of interest None.

Appendix 1

High-risk surgery

1. Aortic vascular surgery
2. Peripheral vascular surgery
3. Prolonged procedures associated with large fluid shifts or blood loss (any intraabdominal procedures such as bowel resection, which is 6 h in duration, other than appendectomy; any procedures with blood loss >1,000 ml; radical cystectomy with ileal loop) are high risk.

Intermediate-risk surgery

1. Carotid endarterectomy
2. Head and neck surgery (ear–nose–throat surgery)
3. Intraperitoneal and intrathoracic surgeries (total pneumonectomy is high risk; lobectomy and partial lung resection are intermediate risk)
4. Prostate surgery (TURP and radical prostatectomy except when the latter involves large blood loss as defined previously)
5. Orthopedic surgery
6. One- to two-level laminectomies (multiple levels with spinal fusion with blood loss >1,000 ml are high risk)
7. Craniotomies with blood loss <1,000 ml, parotidectomy, radical neck dissection, and parathyroidectomy.

Low-risk surgery

1. Breast surgery
2. Plastic surgery
3. Any “superficial” surgeries, including voice prosthesis; inguinal hernia; endoscopic surgeries.

Appendix 2

Standardized direct and indirect effects on pain and opioid dose

Effect	Direct	Indirect	Total
Pre-op pain			
Gender (female)	0.129*		0.129*
Use of pre-op opioids	0.262***		0.262***
Pre-op TICS over 30	−0.097 ⁺		−0.097 ⁺
Geriatric Depression Scale	0.110*		0.110*
Pain on POD1			
Pre-op pain	0.206***		0.206***
Age over 80	−0.111*		−0.111*
High ASA PS	0.144**		0.144**
Gender (female)	0.138**	0.027*	0.165***
Geriatric Depression Scale		0.023 ⁺	0.023 ⁺
Use of pre-op opioids	0.212***	0.054**	0.266***
IV-PCA analgesia	0.125**		0.125*
Pre-op TICS over 30		−0.020 ⁺	−0.020 ⁺
Pain on POD2			
Pre-op pain	0.260***	0.085***	0.345***
Pain on POD1	0.389***	0.026*	0.415***
Opioid dose on POD1	0.139**		0.139**
Age over 80		−0.046*	−0.046*
Gender (female)		0.102***	0.102***
High ASA PS		0.060**	0.060**
Geriatric Depression Scale		0.038*	0.038*
Use of pre-op opioids		0.179***	0.179***
IV-PCA analgesia		0.097***	0.097***
Pre-op TICS over 30		−0.034 ⁺	−0.034 ⁺
High surgical risk	0.124**		0.124**
Opioid dose on POD1			
Pre-op pain		0.038**	0.038**
Pain on POD1	0.185***		0.185***
Age over 80		−0.021*	−0.021*
Gender (female)		0.030**	0.030**
High ASA PS		0.027*	0.027*
Geriatric Depression Scale		0.004 ⁺	0.004 ⁺
Use of pre-op opioids		0.049**	0.049**
IV-PCA analgesia	0.327***	0.023*	0.350***
Pre-op TICS over 30		−0.004	−0.004
Opioid dose on POD2			
Opioid dose on POD1	0.518***	0.020*	0.538***

Appendix 2 continued

Effect	Direct	Indirect	Total
Pre-op pain		0.070***	0.070***
Pain on POD1		0.156***	0.156***
Pain on POD2	0.145**		0.145**
Age over 80		−0.017*	−0.017*
Gender (female)		0.031**	0.031**
High ASA PS	0.108*	0.022*	0.130**
Geriatric Depression Scale		0.008 ⁺	0.008 ⁺
Use of pre-op opioids		0.051***	0.051***
IV-PCA analgesia		0.196***	0.196***
Pre-op TICS over 30		−0.007 ⁺	−0.007 ⁺
High surgical risk		0.018*	0.018*

Geriatric Depression Scale, opioid dose on POD1, and opioid dose on POD2 were log transformed

ASA PS American Society of Anesthesiologists Physical Status Classification, NRS numeric rating scale, IV-PCA intravenous patient-controlled analgesia, POD postoperative day, Pre-op preoperative, SD standard deviation, TICS telephone interview of cognitive status
*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, + $P < 0.10$

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