Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

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Objective: Acute postoperative pain intensity is associated with persistent postsurgical pain (PPP) risk. However, it remains unclear whether acute postoperative pain intensity mediates the relationship between clinical factors and persistent pain.

Materials and Methods: Participants from a mixed surgical population completed the Brief Pain Inventory and Pain Catastrophizing Scale before surgery, and the Brief Pain Inventory daily after surgery for 7 days and at 30 and 90 days after surgery. We considered mediation models using the mean of the worst pain intensities collected daily on each of postoperative days (PODs) 1 to 7 against outcomes of worst pain intensity at the surgical site endpoints reflecting PPP (POD 90) and subacute pain (POD 30).

Results: The analyzed cohort included 284 participants for the POD 90 outcome. For every unit increase of maximum acute postoperative pain intensity through PODs 1 to 7, there was a statistically significant increase of mean POD 90 pain intensity by 0.287 after controlling for confounding effects. The effects of female versus male sex ($m = 0.212$, $P = 0.034$), pancreatic/biliary versus colorectal surgery ($m = 0.459$, $P = 0.012$), thoracic cardiovascular versus colorectal surgery ($m = 0.31$, $P = 0.038$), every minute increase of anesthesia time ($m = 0.001$, $P = 0.038$), every unit increase of preoperative average pain score ($m = 0.012$, $P = 0.015$), and every unit increase of catastrophizing ($m = 0.044$, $P = 0.042$) on POD 90 pain intensity were mediated through acute PODs 1 to 7 postoperative pain intensity.

Discussion: Our results suggest the mediating relationship of acute postoperative pain on PPP may be predicated on select patient and surgical factors.

Key Words: acute pain, chronic pain, mediation analysis, perioperative, surgery

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Moderate to severe postoperative pain afflicts upward of 80% of surgical patients each year.[1,2] Depending on the type of surgery, between 20% and 56% of patients will go on to report moderate to severe persistent postoperative pain.[3] Numerous prior reports have associated high, early, acute postoperative pain intensity with the development of chronic postsurgical pain.[4–7] The transition from acute to persistent pain carries important public health ramifications given the high number of chronic pain patients whose principle analgesic remains chronic opioid therapy and the risks of addiction and death associated with opioid therapies.[8–11]

Despite decades of research associating acute postoperative pain intensity with the development of persistent postsurgical pain (PPP), our understanding of this relationship in the clinical perioperative population remains incomplete.[12–18] One possibility is that prolonged and/or high-impact, acute pain leads to central sensitization and chronification of pain.[19,20] Another possible explanation is that surgery incites a mechanism leading to PPP, but the observed increase in acute postoperative pain intensity is an artifact of that process rather than a causal mechanism. A third option, among many others, is that acute pain mediates the development of persistent pain in certain circumstances, and/or through interaction with other mechanisms.

Regardless, a robust, randomized clinical trial design that randomizes a subset of the study sample to a "suffer" category of high acute postoperative pain intensity is unethical with existing clinical, analgesic, and statistical methodologies. One approach to address the nature of this relationship is through the use of mediation analyses.[21,22]

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In this model, the analysis can test whether an independent variable, such as type of surgery, directly influences the dependent variable, such as PPP, or whether the independent variable instead influences a mediator variable such as acute pain intensity, which itself influences the dependent variable of PPP. Variants of the mediation approach may incorporate "third variables" such as confounders and moderators that can bias the relationships involved in the model. Such mediation analyses serve an important initial step to determining, or refuting, potential causal relationships between acute postoperative pain intensity and the risk of PPP.

Here, we examine the mediating role of acute postoperative pain intensity in the development of persistent postoperative pain in a mixed surgical cohort. We hypothesized that the effects of clinical factors (eg, age, sex, preoperative pain) on persistent postoperative pain could be mediated by acute postoperative pain intensity within the first 7 days following surgery, after controlling for confounding factors. To address this hypothesis, we considered mediation experiments using the mean of the worst pain intensities on each of postoperative days (PODs) 1 to 7, against outcomes of worst pain intensity at the surgical site endpoints reflecting PPP (POD 90) and subacute pain (POD 30).

MATERIALS AND METHODS

This study was a prospective cohort of a mixed surgical population that aimed to investigate how the temporal dynamics of acute postoperative pain are associated with the development of persistent postoperative pain. The protocol (IRB 201500153) was approved by the University of Florida Institutional Review Board-01 and registered at ClinicalTrials.gov (NCT02407743; date of registration: April 3, 2015) before study initiation, participant enrollment, and data collection. This analysis represented an interim report while awaiting follow-up at longer-term endpoints. This article adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[23]

Study Participants

Study participants were patients receiving elective, major urologic, colorectal, pancreatic/biliary, thoracic, spine, or orthopedic surgery with an anticipated postoperative admission. Inclusion criteria included above 18 years of age, an anticipated length of stay of 72 hours or longer, and expected postoperative survival of longer than 6 months. The restriction of surgical procedures of length of stay >72 hours was intended to exclude minor surgical procedures that may have a lower incidence of higher intensity acute and PPP. Exclusion criteria included an anticipated need for prolonged postoperative intubation (>24 h), urgent or emergent surgical procedure, or inability to understand or participate in questionnaires, surveys, or data collection. All participants underwent surgery at UF Health Shands Hospital between November 2015 and September 2018. A convenience sample of patients was screened and recruited within the presurgical clinic by trained research coordinators, generally 1 to 3 weeks before surgery. Patients were compensated for their participation, with compensation provided following enrollment and at study completion.

Preoperative Pain and Pain Management

Patients undergoing colorectal, pancreatic/biliary, thoracic, and orthopedic surgeries were generally offered actively managed perineural, paravertebral, or neuraxial analgesic interventions as part of a multimodal analgesic strategy using a standardized framework linked to surgical procedures. While this resulted in a certain loss of analgesic information, the linkage to surgical procedures offered a limited degree of intraprocedure consistency. As the study incorporated a mixed surgical cohort, comparison of regional anesthetic use across surgical services was unfortunately problematic for the mediation analysis. Patients with chronic pain were not systematically excluded, and baseline preoperative mean pain intensities were included as a covariate to account for the heterogeneous pain characteristics that often lead to surgical consultation.

In general, all surgical patients in the cohort, except those receiving spine surgery, received neuraxial or perineural catheters 1 to 3 hours before surgery according to procedure-specific institutional guidelines. Peripheral and neuraxial catheters were generally maintained for 1 to 3 days after surgery, including daily trials off beginning on POD 1 or 2 depending on patient progression with physical therapy, comorbidity status, and anticipated length of stay. Abdominal surgery patient epidurals were generally discontinued upon resumption of diet, and thoracic surgery patient epidurals were discontinued after chest tube removal. Ambulatory continuous perineural catheters were typically offered to candidate orthopedic surgical patients departing the hospital before POD 3.

Data Collection

Following enrollment, participants completed a battery of psychological and behavioral assessments before surgery. For this analysis, the key instrument was the Brief Pain Inventory (BPI), which asks participants to indicate the number (0, "No Pain" to 10, "Pain As Bad As You Can Imagine") that best describes their pain on the average, worst, and least in the last 24 hours.[24] Patients were assessed with the BPI before surgery, as well as each POD following surgery through POD 7 and again at PODs 30 and 90. The BPI was administered by a trained research coordinator in the patient's hospital room each day after surgery; in the event a patient was discharged before POD 7, the research coordinator contacted the participant by telephone to complete the assessment. The BPI at POD 30 and 90 was similarly assessed; values were considered valid if the patient was able to complete the assessment at the 30-day and 90-day time points within 1 week of the target date.

Sociodemographic and clinical variables included age, sex, type of surgery, duration of surgery, preoperative mean pain intensity assessed through the BPI, Charlson Comorbidity Index, and catastrophizing measured using the Pain Catastrophizing Scale-13.[25,26] For the categorical variables of sex and type of surgery, the reference categories were set to female and colorectal surgery. This parsimonious selection of a limited array of sociodemographic variables represented a compromise given the anticipated degrees of freedom encountered in the mediation analysis.

Missing data were managed through row-wise elimination of participants and were considered missing at random. Separate cohorts were used for POD 30 and POD 90 outcomes given the loss of POD 90 outcomes relative to POD 30 outcomes because of loss at follow-up. Given the potential for a selection bias of at-risk surgical procedures,

analyses, and interpretations were restricted to the surgical procedures examined here. Observer bias was addressed using objective surveys administered in electronic format requiring minimal input from research coordinators.

Statistical Analysis

Mediation analyses generally involve how an intermediate variable affects the exposure (of interest)'s effects on an outcome.[27] For instance, if we were to study diet's effects on heart disease, we would traditionally consider how much the total diet's effects on heart disease is because of diet. In this regard, we may wish to understand whether diet directly led to heart disease, or whether diet led to weight gain and then weight gain led to heart disease. The relative direct and indirect (eg, mediated through diet's effect on weight gain) effects can be further adjusted through the effects of other covariates (eg, age) on direct (eg, diet) and mediating (eg, weight gain) factors, as well as the outcome (eg, heart disease). Apropos of this study, we are specifically interested in the relative direct versus indirect effects of established patient and surgical factors, including associations with acute pain intensity, on the development of PPP. We should note that even in the case of mediation through weight gain, the weight gain itself may instead lead to high blood pressure, which may also separately mediate the effect on heart disease; this recursive approach to mechanistic investigations remains a common challenge and opportunity in mediation and causal inference. It also applies to the relationship between acute pain intensity and PPP; even if present, there are likely additional mediators related to acute pain intensity underlying any such effect.

The primary objective was to investigate the direct and indirect (ie, through mediation) effects of demographic factors (eg, age, sex) and clinical variables (eg, surgery type, Charlson Comorbidity Index, duration of surgery, preoperative mean pain intensity, catastrophizing) on the outcome of worst daily pain intensity 30 days (POD 30) and 90 days (POD 90) following surgery. For each outcome, we used the average of the worst pain intensity ratings for each of PODs 1 to 7 as the mediator. In other words, we examined how much of the total effects of each demographic and clinical variable was because of each of the variable directly and indirectly (through acute pain) on the POD 30 and POD 90 pain intensity outcomes by controlling other confounding factors. Confounders included age, sex, surgical duration, Charlson Comorbidity Index, preoperative mean pain intensity, and catastrophizing and were included in all models. For our primary hypothesis, we adopted the mean of the worst pain intensity from each of PODs 1 to 7 as the mediation factor, with the purpose of describing how patient and clinical characteristics (covariates) would affect the development of persistent postoperative pain (outcome) at POD 90 through the postoperative acute pain experience (mediator). Importantly, the mediator data were derived from the collection of daily BPI assessments as described above. Our secondary hypothesis used POD 30 as an indicator of subacute pain.[28]

We included all participants who met the following 3 criteria: (1) completed data for all 7 baseline covariates (*X*); (2) completed BPI assessment at PODs 30 and 90; (3) at least 2 BPI pain intensity assessments available from initial postoperative time point through POD 7.

To describe how an independent variable (*X*) affects outcome (*Y*) directly and indirectly (ie, through the mediator [*M*]), we adopted the following mediation analysis

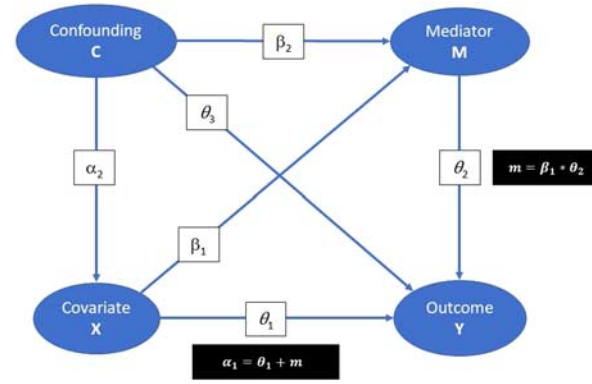

FIGURE 1. Overview of the approach to mediation analysis. After accounting for confounding factors (*C*), patient and clinical covariates (*X*) were examined for both direct association with the outcome of persistent postoperative pain at 30 days following surgery (*Y*) as well as through a mediating effect (*M*) of acute postoperative pain intensity in postoperative days 1 to 7. full color online

models[29–31] by adjusting the confounding factors (***C***):

$$(1)\ \mathrm{E}(Y|X,\ C) = \alpha_0 + \alpha_1 X + \alpha_2' C$$

$$(2)\ \mathrm{E}(M|X,\ C) = \beta_0 + \beta_1 X + \beta_2' C$$

$$(3)\ \mathrm{E}(Y|X,\ M,\ C) = \theta_0 + \theta_1 X + \theta_2 M + \theta_3' C$$

In this mediation modeling scheme, the relationship among different variables is depicted per Figure 1.

Here, θ_1 is the direct effect of *X* on outcome *Y*, while the indirect effect of *X* (through mediator *M*) is defined as: $m = \beta_1 \times \theta_2$. The total effects of covariate *X* on outcome *Y* is a sum of indirect (*m*) and direct (θ_1) effects and is represented as α^1. Although the estimate for each parameter in the above models can be obtained directly from multiple regression analysis, the variance estimate of indirect effect *m* is not straightforward because of the correlation of β_1 estimate and θ_2 estimate. To address this, we adopted the empirical bootstrap with replacement to obtain valid estimates of the variance of mediation effect estimate *m*, with 10,000 replications.

Analyses were conducted using the open source statistical software package R (version 3.5.0). *P*-values are reported based on 2-sided statistical hypothesis tests. Missing data were considered missing at random; no imputations were performed given the nature of the confounding structures used in the mediation analysis. No preanalysis power analyses were conducted given the difficulties of power analyses with mediation effects. Parameter estimates using 3 mediators are summarized in Tables 1 and 2.

RESULTS

The analysis included 284 participants for the POD 90 outcome and 311 participants for the POD 30 outcome (see STROBE flowchart, Fig. 2). For patients who completed data collection through POD 7, 88% of participants completed follow-up through POD 30 and 80% through POD 90. For the POD 90 outcome, the most common surgeries were colorectal (25.4%) and thoracic surgery (18.7%; Table 3). Patients reported a low Charlson Comorbidity Index (2.4 ± 2.9) and low preoperative average pain intensity (2.3 ± 2.9). Pain catastrophizing was generally low

TABLE 1. Parameter Estimates of Direct and Mediated Modeling Effects on Worst Pain at Postoperative Day 90

Covariate	α_1	*P*	β_1	*P*	θ_1	*P*	θ_2	*P*	*m*	*P*
Age	−0.058	<0.001	−0.002	0.884	−0.057	<0.001	0.287	<0.001	−0.001	0.864
Male	−0.242	0.452	−0.738	0.003	−0.03	0.925	0.287	<0.001	−0.212	0.034
Spine surgery	2.24	<0.001	−0.156	0.721	2.285	<0.001	0.287	<0.001	−0.044	0.736
Orthopedic surgery	1.338	0.011	1.604	<0.001	0.877	0.095	0.287	<0.001	0.459	0.012
Pancreas and biliary surgery	1.363	0.005	1.067	0.004	1.056	0.027	0.287	<0.001	0.31	0.038
Thoracic surgery	0.846	0.091	−0.153	0.692	0.89	0.069	0.287	<0.001	−0.043	0.71
Urologic surgery	0.004	0.013	0.004	0.01	0.003	0.055	0.287	<0.001	0.001	0.038
Duration of surgery	0.015	0.808	−0.04	0.386	0.026	0.656	0.287	<0.001	−0.011	0.481
CCI	0.01	0.532	0.042	0.001	−0.002	0.893	0.287	<0.001	0.012	0.015
Preoperative mean pain intensity (BPI)	−0.058	<0.001	−0.002	0.884	−0.057	<0.001	0.287	<0.001	−0.001	0.864
Catastrophizing (PCS-13)	0.22	0.002	0.153	0.006	0.176	0.013	0.287	<0.001	0.044	0.042

Surgical procedure covariates use colorectal surgery as reference class.
BPI indicates Brief Pain Inventory; CCI, Charlson Comorbidity Index; PCS, Pain Catastrophizing Scale.

(25.7 ± 11.9). The outcome of interest, worst pain intensity on POD 90 as measured by the BPI, was low (mean 1.9 ± 2.9) but spanned the entire gamut of measured intensities. Similar distributions of participant characteristics and outcomes were seen for the POD 30 endpoint.

The mediator for each outcome was defined as the maximum pain intensity on PODs 1 to 7 (Fig. 3). For POD 90, the mean of the maximum pain intensities on PODs 1 to 7 was 6.12 ± 2.27 (Fig. 3A). For POD 30, the mean of the maximum pain intensities on PODs 1 to 7 was 6.15 ± 2.24 (Fig. 3B).

Mediation Effects of Worst Acute Pain on POD 90

Table 1 shows the parameter estimates for the direct and indirect effects on pain intensity POD 90 when the mediator is defined as the maximum pain intensity on PODs 1 to 7 per the daily assessment of BPI. For every unit increase of maximum acute postoperative pain intensity (ie, PODs 1 to 7), there was a statistically significant increase of mean POD 90 pain by 0.287 when all other clinical factors remain unchanged (Fig. 4A).

Age had a highly significant negative total effect on the worst 3-month pain intensity ($\alpha_1 = -0.058$, $P < 0.001$). Of this total effect of age, the direct effects were negative and significant ($\theta_1 = -0.057$, $P < 0.001$) but the indirect effect through maximum acute pain was statistically insignificant ($m = -0.001$, $P = 0.864$) after controlling for confounding factors of sex, surgery type, surgical duration, Charlson Comorbidity Index, preoperative pain intensity, and catastrophizing. Overall, each year increase of age led to a 0.057-unit decrease of worst 3-month pain intensity directly, but a statistically insignificant 0.001-unit decrease of worst 3-month pain intensity indirectly.

Compared with colorectal surgery patients, spine surgery patients had significantly higher worst 3-month pain intensity ($\alpha_1 = 1.562$, $P = 0.030$). Of this overall effect, the direct effects were predominant and statistically significant ($\theta_1 = 1.528$, $P = 0.030$), while the indirect effect was insignificant ($P = 0.864$) after controlling for confounding factors. Similarly, orthopedic surgery patients had significantly higher worst 3-month pain intensity ($\alpha_1 = 2.24$, $P < 0.001$) than colorectal surgery patients. Here, the direct effects were significant ($\theta_1 = 2.285$, $P < 0.001$), and the indirect effect was insignificant ($m = -0.044$, $P = 0.736$) while controlling other confounding factors.

Pancreatic/biliary surgery patients had significantly higher worst 3-month pain intensity ($\alpha_1 = 1.338$, $P = 0.011$) than the reference class of colorectal surgery. However, contrary to the relationships seen in spine and orthopedic surgeries, in pancreatic/biliary surgery the direct effect was insignificant ($\theta_1 = 0.877$, $P = 0.095$), while the indirect effect was significant ($m = 0.495$, $P = 0.012$) after controlling for confounders. In other words, patients undergoing pancreatic/biliary surgery experienced 1.338 units higher worst 3-month pain intensity; of this difference, 0.877 units were directly due the type of surgery, while a 0.459-unit difference was mediated through the maximum acute pain on PODs 1 to 7.

Compared with colorectal surgery patients, thoracic surgery patients had significantly higher worst 3-month pain intensity ($\alpha_1 = 1.363$, $P = 0.005$), of which both the direct effect ($\theta_1 = 1.056$, $P = 0.027$) and the indirect effect

TABLE 2. Parameter Estimates of Direct and Mediated Modeling Effects on Worst Pain at Postoperative Day 30

Covariate	α_1	*P*	β_1	*P*	θ_1	*P*	θ_2	*P*	*m*	*P*
Age	−0.061	<0.001	−0.008	0.445	−0.058	<0.001	0.415	<0.001	−0.003	0.462
Male	−1.067	0.003	−0.633	0.009	−0.805	0.022	0.415	<0.001	−0.26	0.022
Spine surgery	1.207	0.126	0.26	0.621	1.1	0.147	0.415	<0.001	0.102	0.632
Orthopedic surgery	1.63	0.009	−0.225	0.589	1.723	0.004	0.415	<0.001	−0.097	0.568
Pancreas and biliary surgery	0.255	0.663	1.348	0.001	−0.304	0.597	0.415	<0.001	0.56	0.005
Thoracic surgery	1.954	<0.001	0.867	0.017	1.594	0.003	0.415	<0.001	0.365	0.034
Urologic surgery	0.137	0.811	−0.15	0.696	0.199	0.718	0.415	<0.001	−0.065	0.697
Duration of surgery	0.006	0.001	0.003	0.011	0.005	0.008	0.415	<0.001	0.001	0.038
CCI	−0.111	0.087	−0.073	0.091	−0.081	0.198	0.415	<0.001	−0.03	0.168
Preoperative mean pain intensity (BPI)	−0.003	0.869	0.033	0.004	−0.017	0.319	0.415	<0.001	0.014	0.012
Catastrophizing (PCS-13)	0.183	0.022	0.133	0.012	0.127	0.099	0.415	<0.001	0.056	0.032

Surgical procedure covariates use colorectal surgery as reference class.
BPI indicates Brief Pain Inventory; CCI, Charlson Comorbidity Index; PCS, Pain Catastrophizing Scale.

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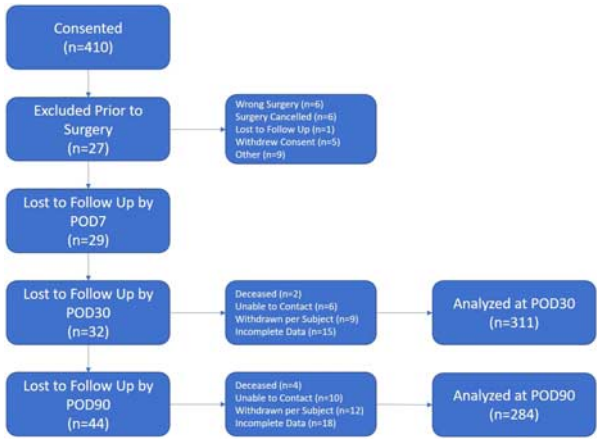

FIGURE 2. Participant flow through study. POD indicates postoperative day. full color online

($m = 0.310$, $P = 0.038$) were significant. Thus, patients undergoing thoracic surgery had 1.363 units higher worst 3-month pain intensity; 1.056 units were directly because of surgery type, while the 0.310-unit difference was mediated indirectly through the maximum acute pain on PODs 1 to 7.

The duration of surgery had significant ($\alpha_1 = 0.004$ units per minute, $P = 0.013$) positive total effects on the worst 3-month pain intensity. The direct effect ($\theta_1 = 0.003$, $P = 0.055$) was insignificant, but the indirect effect ($m = 0.001$ units per minute, $P = 0.038$) was positive and significant.

Catastrophizing also had a significant ($\alpha_1 = 0.22$, $P = 0.002$) positive total effect on the 3-month worst pain intensity. With catastrophizing, the direct effects ($\theta_1 = 0.176$, $P = 0.013$) and indirect effects ($m = 0.044$, $P = 0.042$) were both significant. That is, for every unit increase of catastrophizing score, it led to a 0.220-unit increase of 3-month worst pain intensity. Of this total effect, a 0.176-unit increase of 3-month worst pain intensity was directly because of the increase of catastrophizing score, while a 0.044-unit increase of 3-month worst pain intensity was indirectly mediated through the maximum acute pain on PODs 1 to 7.

Mediation Effects of Worst Acute Pain on POD 30

Table 2 shows the parameter estimates for the direct and indirect effects on pain intensity at POD 30 when the mediator is defined as the maximum pain intensity on PODs 1 to 7 as measured by the daily BPI assessment. For every unit increase of maximum acute postoperative pain intensity (ie, PODs 1 to 7), there was a statistically significant increase of mean POD 30 pain by 0.415 when all other clinical factors remain unchanged (Fig. 4B).

Age had highly significant negative total effects on the 1-month worst pain ($\alpha_1 = -0.061$, $P < 0.001$). Of those, the direct effects were negative and significant ($\theta_1 = -0.058$, $P < 0.001$) while the indirect effect (through maximum acute pain) was negative yet insignificant ($m = -0.003$, $P = 0.462$) after controlling for confounders. In other words, every year increase of age led to a 0.058-unit decrease of the 1-month worst pain intensity directly and a 0.003-unit decrease of 1-month worst pain intensity indirectly.

Overall, males had significantly ($\alpha_1 = -1.067$, $P = 0.003$) lower 1-month worst pain intensity than females. Here, the direct effect was significant ($P = 0.022$) as was the indirect effect ($m = -0.260$, $P = 0.022$). In total, males had a 1.067 unit lower 1-month worst pain intensity than females. Among the total effect, 0.805 units were directly because of sex, while 0.260 units were indirectly mediated through the maximum acute pain on PODs 1 to 7.

Compared with colorectal surgery patients, orthopedic surgery patients reported significantly higher worst 1-month worst pain intensity ($\alpha_1 = 1.630$, $P < 0.001$). The direct effect was significant ($\theta_1 = 1.723$, $P = 0.004$), but the indirect effect remained insignificant ($m = -0.097$, $P = 0.568$). Thoracic surgery patients also had significantly higher 1-month worst pain intensity ($\alpha_1 = 1.954$, $P < 0.001$) where both direct

TABLE 3. Sociodemographic and Pain Characteristics of Study Cohort

	Postoperative Day 90				Postoperative Day 30			
Variable	**Count**	**Percentage**			**Count**	**Percentage**		
Participants	284				311			
Sex								
Female	144	50.7			160	51.4		
Male	140	49.3			151	48.6		
Surgery								
Colorectal	72	25.4			77	24.8		
Spine	21	7.4			23	7.4		
Orthopedics	45	15.8			52	16.7		
Pancreas and biliary	41	14.4			45	14.5		
Thoracic	53	18.7			60	19.3		
Urology	52	18.3			54	17.4		
Variable	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Age (y)	58.7	12.5	22	83	58.8	12.5	22	83
Duration of surgery (min)	190.4	94.8	13	523	189.7	95.9	13	523
Charlson Comorbidity Index	2.4	2.9	0	11	2.5	2.9	0	11
Preoperative mean pain intensity (BPI)	2.3	2.9	0	10	2.4	3	0	10
Catastrophizing (PCS-13)	12.7	11.9	0	52	13.4	12.4	0	52
Worst pain intensity on postoperative day 90 (BPI)	1.9	2.9	0	10	3.20	3.3	0	10

BPI indicates Brief Pain Inventory; PCS, pain catastrophizing scale.

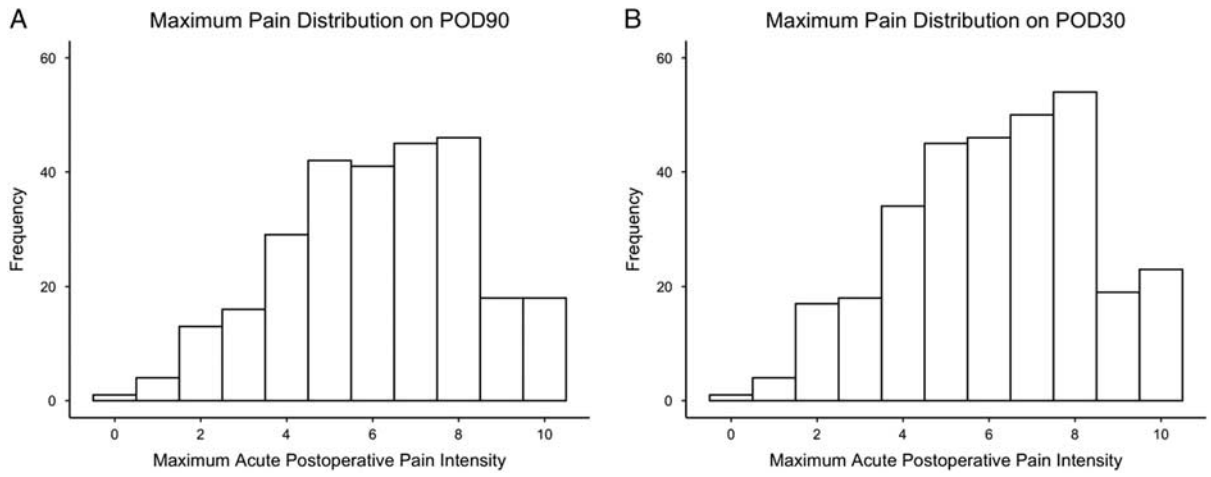

FIGURE 3. Distribution of mediator effects. Each mediator was calculated using daily maximum pain intensities as assessed by the Brief Pain Inventory. Separate mediators were considered for the outcome of worst pain intensity on postoperative day POD 90 (A) and POD 30 (B).

effects ($\theta_1 = 1.594$, $P = 0.003$) and the indirect effects ($m = 0.365$, $P = 0.034$) were significant.

The duration of surgery had significant ($\alpha_1 = 0.006$, $P = 0.001$) positive total effects on the 1-month worst pain. Both the direct effects ($\theta_1 = 0.005$, $P = 0.008$) and indirect effects ($m = 0.001$, $P = 0.038$) were positive and significant. For every minute increase of anesthesia time, there was a 0.006-unit increase of 1-month worst pain intensity. Of the total effect, a 0.005-unit increase of 1-month worst pain intensity was directly because of the increase of anesthesia time, while a 0.001-unit increase of worst 1-month worst pain intensity was mediated indirectly through the maximum acute pain on PODs 1 to 7.

Catastrophizing had significant ($\alpha_1 = 0.183$, $P = 0.022$) positive total effects on the worst 1-month worst pain. However, the direct effects ($\theta_1 = 0.127$, $P = 0.099$) were insignificant, while the indirect effect ($m = 0.056$, $P = 0.032$) was significant.

DISCUSSION

Our results demonstrate that several factors previously associated with the development of PPP, such as sex, type of surgery, and catastrophizing, may be partially or fully mediated through the effects of acute postoperative pain intensity on the first 7 days after surgery. In contrast, after considering the effects of confounding variables and the direct effects of covariates on the intensity of PPP, the influence of acute postoperative pain intensity itself on PPP varied according to the type of surgery. The mediating effect of acute postoperative pain was largely consistent across features for the outcomes of subacute pain at POD 30 and PPP at POD 90, although preoperative pain, duration of surgery, and thoracic surgery had mediating effects through acute postoperative pain at POD 30 but not POD 90 outcomes.

Strictly speaking, while our results suggest a mediating effect of acute postoperative pain in the development of PPP in select circumstances, this does not necessarily translate to a causal interpretation, although our analysis did adjust for confounding factors with parametric methods, and more robust statistical methods should be adapted in future investigations.[27,32,33] In contrast, the implied temporal directionality of the progression from acute to chronic time points may strengthen the argument that patient and procedural factors associated with PPP development may partially exert their effects through processes reflected by acute pain intensity.[33] Importantly, even this potential for causality remains unclear; a more comprehensive analysis would need to consider clinical decisions, including analgesics, early mobilization, and physical therapy, each of which could feasibly influence acute pain and PPP risk through plausible mechanisms.

Overall, we identified a significant association between the mean of the maximum acute postoperative pain intensity on PODs 1 to 7 and worst pain intensity over the past 24 hours at POD 90, such that each unit increase in the PODs 1 to 7 maximum pain was associated with a 0.287-point increase of the 0 to 10 scale at the POD 90 endpoint. We observed an even greater association between PODs 1 to 7 and POD 30 time points, with a 0.415-point increase at POD 30 for each unit increase in the mean of the maximum acute postoperative pain intensity on PODs 1 to 7. These findings partially align with those of Fletcher et al,[34] who found a 10% increase in the percent of time spent in severe acute postoperative pain was associated with a 24% greater incidence of PPP at 6 months after surgery, although no association was found between PPP risk and the worst acute postoperative pain score.

Prior research has repeatedly demonstrated that certain procedures have a greater association with persistent postoperative pain, even to the extent that different techniques for a given procedure are also associated with different pain outcomes.[6,35] Our findings identified the strongest overall linkages with PPP in spine surgery, orthopedic surgery, and pancreatic/biliary surgery. Of these, only orthopedic and pancreatic/biliary surgery had indirect effects partially mediated through acute postoperative pain, while spine surgery effects appeared to be entirely mediated through direct association. While urologic procedures were associated with direct and indirect effects on POD 90 pain intensity, the very low overall difference of 0.004 is unlikely to be of clinical significance.

Surprisingly, we did not identify an independent direct or indirect effect of thoracic surgery on the intensity of pain at POD 90. However, with respect to subacute pain, thoracic surgery had the strongest overall association with POD 30 pain intensity and included direct and indirect

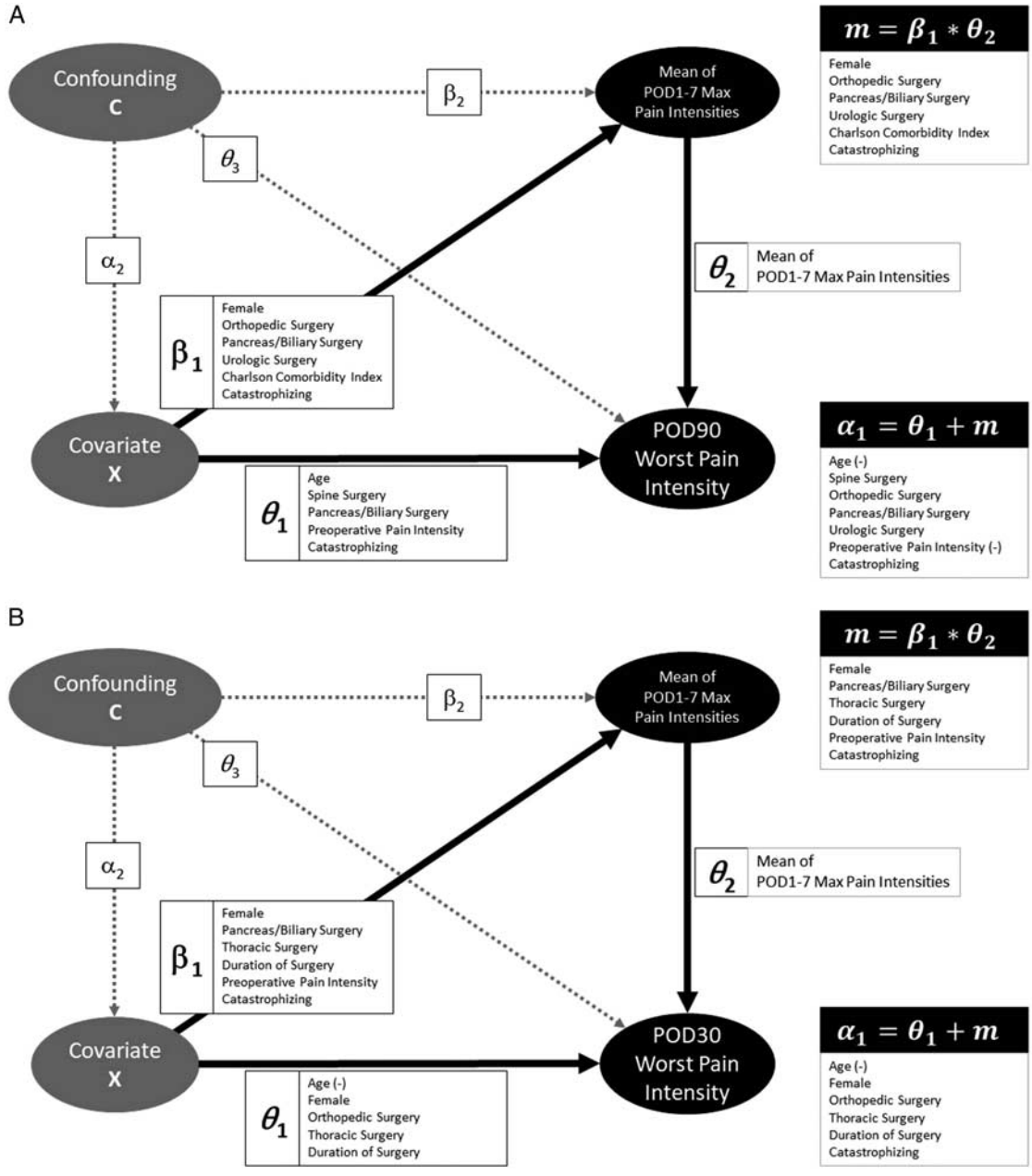

FIGURE 4. Relationships among contributing factors for mediating and direct effects. Features with statistically significant coefficients of the mediating model are listed for each term in the mediating model for postoperative day (POD) 90 (A) and POD 30 (B) outcomes.

effects. We postulate that this departure from prior associations between thoracic surgery and PPP may reflect the increasingly minimal approach to thoracic surgical procedures through robotic techniques.[36] The lack of power to replicate such findings may also reflect the heterogeneity of our surgical populations, which were intended to represent a wide range of surgical tissue injury mechanisms and to compare different trajectories and measurements, albeit at the cost of intraservice specificity.

The mixed results of direct and indirect associations for certain types of surgeries with the POD 90 outcomes suggest that acute pain therapy could theoretically modify the risk of persistent postoperative pain developing from certain procedures (eg, orthopedic, pancreatic, and biliary surgery) but not others, perhaps by alleviating windup and ensuing central sensitization as noted in numerous mechanistic models.[20,37–39] Indeed, limited data have identified associations between analgesic and anesthetic interventions in the intraoperative and early postoperative period and improved outcomes related to PPP in certain surgical procedures.[40–42] Alternatively, our results also raise the possibility that for some surgical procedures (eg, spine), the risk of persistent postoperative pain occurs independently of the acute postoperative pain intensities and may increase the difficulty of examining the role of acute pain interventions following such surgeries.

Our analyses included the duration of surgery as a covariate separate from the type of surgery. Currently, there are no objective quantifications of surgery-induced tissue trauma that can be linked to postoperative pain sequelae, so duration of surgery was used as a conceptual proxy. This also allowed our analyses to partially control for different surgical duration distributions inherent to different surgery types and suggests that surgical duration may be an independent contributor to POD 90 and POD 30 pain outcomes through effects on acute pain intensity. Our results align with prior work that identified surgical invasiveness as an independent risk factor of PPP following thoracotomy and breast cancer surgery.[43,44]

Prior studies have repeatedly indicated that pain catastrophizing is linked with an increased risk of both acute and chronic postsurgical pain.[45–50] Our results suggest that for both subacute and chronic postoperative pain outcomes, pain catastrophizing exerts its influence through direct effects as well as through effects mediated in acute postoperative pain intensities. For POD 90 outcomes, the direct effect coefficient was 4 times greater than that of the indirect effect of acute postoperative pain intensity on PODs 1 to 7. Masselin-Dubois et al[51] investigated whether the association of catastrophizing and chronic postsurgical pain differed for total knee arthroplasty versus breast cancer surgery and showed that pain magnification independently predicted chronic postsurgical pain and was not dependent on arthroplasty versus breast surgery. Our results further generalize this relationship across a wider range of surgeries, although the current report did not differentiate among catastrophizing domains.

We selected worst pain intensity over the past 24 hours as POD 30 and POD 90 endpoints given that the maximal pain may impart greater suffering than aggregate assessments of pain within the BPI. Among a number of potential pain assessment tools, Atkinson et al[52] identified "pain at its worst in the last 24 hours" in the BPI as complying with US Food and Drug Administration guidance on using patient-reported outcomes and assessing analgesic treatment effects. Across multiple validation studies of the BPI, "pain at its worst in the last 24 hours" has been consistently demonstrated as the greatest internal consistency of the BPI elements with the Cronbach α coefficients ranging from 0.77 to 0.90 across a wide range of cultures.[53,54]

There were several limitations inherent to the design of this study. Our relatively small sample size limited the number of factors available for analyses, including preoperative opioid use, duration of preoperative pain, and additional specification on surgical procedure codes. While mediation analyses may offer insight into the relative direct versus mediated effect of features on postoperative pain outcomes, it is important to differentiate such insights from causal models. Our results cannot in any way prove that acute postoperative pain causes subsequent postoperative outcomes, pain-related or otherwise.[55] Given the nature of mediation analyses, power analyses are not feasible, thus associations that did not reach statistical significance must be considered within the context of increased uncertainty of type II errors. In addition, we included bootstrapping to improve the estimation of the variance of mediation effects. Another limitation concerns the nature of clinical pain intensity assessments; high pain intensity following surgery in both acute and chronic time frames may result from high levels of nociception despite aggressive analgesic titration, relatively low nociception in the setting of grossly inadequate analgesia, or biopsychosocial modulators despite relatively low nociception and aggressive analgesia. Future work on mediation and causality will need to simultaneously consider biopsychosocial effects on reported perioperative pain intensity for acute and chronic time points. In addition, our definition of PPP focused exclusively on pain intensity, and future research is needed that incorporates the functional impact of pain into this case definition.

CONCLUSIONS

In conclusion, our results highlight the role of surgery type in partitioning among direct versus mediating effects on longer-term pain outcomes. These results suggest that we may need to consider acute and chronic pain outcomes as separate mechanistic entities depending on select patient and surgical factors, and that in certain clinical scenarios, it may be that aggressive treatment of acute postoperative pain intensity itself may not confer direct protection from persistent postoperative pain. While the mediation analyses successfully partitioned the direct effects of patient and surgical factors on the development of subacute and chronic postoperative pain outcomes from those mediated through acute postoperative pain intensity on PODs 1 to 7, this work also highlighted the need to further extend this line of investigation to consider causal effects models that can more conclusively examine the nature of these relationships.

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