OBSERVATIONAL STUDY

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Risk Factors for Increased Opioid Use During Postoperative Intensive Care

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IMPORTANCE: In the ICU, opioids treat pain and improve ventilator tolerance as part of an analgosedation approach. Identifying predictors of opioid consumption during the ICU course might highlight actionable items to reduce opioid consumption.

OBJECTIVES: To identify risk factors for opioid use during a postoperative ICU course.

DESIGN, SETTING, AND PARTICIPANTS: Patients enrolled in the Michigan Genomics Initiative single-center prospective observational cohort study completed baseline preoperative sociodemographic and mental/physical health questionnaires and provided blood samples for genetic analysis. Included patients were 18 years old and older, admitted to ICU postoperatively, and received opioids postoperatively.

MAIN OUTCOMES AND MEASURES: The primary outcome was ICU mean daily oral morphine equivalent (OME) use. The association between OME and phenotypic risk factors and genetic variants previously associated with pain were analyzed through univariable and multivariable linear regression models.

RESULTS: The cohort consisted of 1865 mixed-surgical patients with mean age of 56 years (SD, 15 yr). Preoperative opioid users were more likely to continue to receive opioids throughout their ICU stay than opioid-naive patients. OME ($\log_{10}$ scale) was most strongly associated with ICU mechanical ventilation ($\beta = 0.27$; 95% CI, 0.15–0.38; $p < 0.0001$; effect size 1.85 for receiving > 24 hours of mechanical ventilation), preoperative opioid use ($\beta = 0.22$; 95% CI, 0.16–0.29; $p < 0.0001$; effect size 1.67 for receiving preoperative opioids), major surgery ($\beta = 0.21$; 95% CI, 0.12–0.30; $p < 0.0001$; effect size 1.62 compared with minor surgery), and current/former illicit drug use ($\beta = 0.12$; 95% CI, 0.01–0.23; $p = 0.04$; effect size 1.30 for drug use). Younger age, centralized pain, and longer anesthetic duration were also significantly associated with OME but with smaller effect sizes. Selected genetic variants (*FKBP5*, *COMT*, and *OPRM1*) were not associated with OME use.

CONCLUSIONS AND RELEVANCE: Mechanical ventilation and preoperative opioids were the strongest risk factors for postoperative ICU opioid consumption, whereas psychologic factors and genetic variants were not associated.

KEYWORDS: acute postoperative pain; *COMT*; critical care illness; *FKBP5*; *OPRM1*; oral morphine equivalents; post-intensive care syndrome; post-surgical pain; single nucleotide polymorphism

With an improved survival from the ICU (1), many patients are being discharged with an impaired quality of life involving mental health, cognitive, and functional domains, which constitutes post-intensive care syndrome (2). Among this spectrum of impairments, the frequency of persistent pain after an ICU stay varies from 18% to 77% of ICU survivors post-discharge (3–5), and 4% of ICU survivors have been found to develop new persistent opioid use (6).

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KEY POINTS

Question: What are the risk factors for opioid use during a postoperative ICU course?

Findings: Younger age, preoperative opioid use, centralized pain, illicit drug use, major surgery, longer anesthetic duration, and ventilator use in the ICU were associated with increased opioid use during the postoperative ICU course.

Meaning: Preoperative opioid use, surgical characteristics, and postoperative mechanical ventilation were associated with increased oral morphine equivalent use during a postoperative ICU course.

Opioids are used frequently in the ICU for the treatment of pain and for endotracheal tube/ventilator tolerance, as part of an analgosedation approach to patient care (7–9). High exposure to opioids in the ICU may lead to opioid-induced hyperalgesia, central sensitization of pain, opioid tolerance, and persistent opioid use (10, 11). Focusing on what drives postoperative opioid use during the ICU encounter might identify factors amenable to changes that would reduce opioid consumption.

Several genes have been implicated in pain-related phenotypes, which are important to evaluate in the context of opioid use to treat post-surgical pain in the ICU. Specifically, the catechol-O-methyltransferase (*COMT*) gene and *FK506 binding protein 51* (*FKBP5*) gene have been implicated in the development of chronic pain and somatic symptoms after traumatic events (12, 13). Both genes are involved in the stress response system: COMT is the primary enzyme that metabolizes catecholamines (13) and FKBP5 is a glucocorticoid receptor co-chaperone that influences the hypothalamic pituitary axis (12). Additionally, a variant of the gene encoding opioid receptor μ-1 (OPRM1) has been shown to affect opioid consumption in the postoperative period (14, 15). However, genetic variants associated with increased opioid consumption in the ICU have not yet been elucidated.

The purpose of this study was to describe the use of opioids during a postoperative ICU course and to identify phenotypic and genetic risk factors for increased opioid consumption during the ICU encounter. We hypothesized that preoperative opioid use, higher levels of baseline pain, and sociodemographic and mental health characteristics previously found to be associated with chronic pain would be associated with higher opioid requirements in the ICU. We also hypothesized that a targeted subset of single nucleotide polymorphisms (SNPs) in three genes previously found to be associated with pain outcomes would be risk factors for postoperative ICU opioid consumption.

MATERIALS AND METHODS

Population and Study Design

Patients were enrolled in this single-center prospective observational cohort study between 2012 and 2017 as part of the Michigan Genomics Initiative (MGI), the methodology of which has been previously described (16). MGI is a biorepository of patients over 18 years old who completed a preoperative baseline survey and provided a blood sample for genetic analysis before a surgical procedure at a University of Michigan site. All participants provided informed consent and were enrolled at the time of their preoperative visit. Data collected comprised sociodemographic, pain and mental health questionnaires, and electronic health record data.

ICU admissions were identified through professional billing codes and confirmed in the medical record. Participants were included if they filled out the baseline questionnaire within 60 days before their ICU admission and were admitted to the ICU within 24 hours postoperatively. Patients deceased during the hospitalization were excluded. Additionally, we excluded patients who did not receive opioids during their ICU course because they were likely in the ICU for reasons other than their critical illness, such as serial neurovascular monitoring.

Institutional Review Board (IRB) approval was obtained at the University of Michigan (September 13, 2017 HUM00101589, primary IRB oversight, Sociodemographic and genotypic predictors of chronic pain in patients requiring an ICU course following surgery) and at Duke University (December 10, 2019 Pro00103614). Procedures were followed in accordance with the ethical standards of the IRB on human experimentation and with the Helsinki Declaration of 1975.

Exposures, Outcomes, and Covariates

Baseline Characteristics. Patient baseline sociodemographic characteristics were collected. The presence of preoperative opioid use (yes/no) was determined from their preoperative medication list. Total preoperative opioid doses were not able to be determined because the electronic preoperative medication lists only contained as needed ranges.

The baseline MGI questionnaire contained baseline pain characteristics before surgery assessed with the Brief Pain Inventory (average body pain score, range 0–10) (17), the Michigan Body Map (number of preexisting chronic pain areas, 0–35 areas) (18), and the Pain Detect Neuropathic Pain Scale (–1 to 38) (19). Centralized or nociplastic pain was assessed with the Fibromyalgia Symptom Score (0–31) (20), which is a measure of widespread body pain and has previously been found to predict increased postoperative opioid use after surgeries such as arthroplasty and hysterectomy (21, 22). Psychologic factors were assessed with the Life Satisfaction Scale (23), the Patient-Reported Outcomes Measurement Information System (24), and the Hospital Anxiety and Depression Scale (25) questionnaires (> 8 indicating at least moderate anxiety or depression).

Genetic Data. MGI blood sample collection and genotyping methods were described in detail (16). Blood was collected at the time of surgery and genotyped on an Illumina Infinium CoreExome-24 bead array platform (Illumina, Inc., San Diego, CA). Sample-level quality control was done on a rolling basis, and criteria for excluding samples were genotype-inferred sex not matching the self-reported gender, sample-level call rate less than 99%, and any technical issue. SNPs with Hardy Weinberg $p < 10^{-4}$ within each array were excluded. Genetic ancestry was estimated by principal component analysis and admixture analysis using genome-wide independent variants determined by linkage disequilibrium of r^2 value of less than 0.5. In the current study, six *FKBP5* SNPs, nine *COMT* SNPs (present in three haploblocks spanning the gene), and one *OPRM1* SNP were selected for analysis based on prior associations with pain. The six *FKBP5* SNPs were rs3800373, rs7753746, rs9380526, rs2817040, rs9394314, and rs2817032 (12). The *OPRM1* SNP was rs1799971 (15). The three haploblocks in *COMT* consist of block 1 (rs2020917, rs737865, and rs1544325), block 2 (rs4633, rs4818, rs4680, and rs165774) and block 3 (rs174697 and rs165599) (13). Haplotypes in block 2 corresponded to those previously identified by Diatchenko et al (26) (low pain sensitivity, high pain sensitivity, and average pain sensitivity 1 and 2).

Outcomes. The primary outcome measure was mean daily oral morphine equivalents (OMEs) use in the ICU obtained from the electronic medical record. Mean daily OMEs were calculated by converting all opioids given in the ICU to OMEs (27) and averaging over the number of ICU days in a patient's course. Comparing OMEs is commonly used to analyze opioid consumption (28, 29). Examples of conversions to OME used in this study were: 1 mg oxycodone = 1.5 mg OME, 100 μg parenteral fentanyl = 10 mg OME, 1 mg parenteral hydromorphone = 20 mg OME, and 1 mg parenteral morphine = 3 mg OME. We attempted to extract whether epidurals or regional techniques were used for intraoperative or postoperative analgesia, but these occurrences were very low, and therefore this information was not extracted.

Covariates. Additional covariates included anesthesia duration, and whether patients required greater than 24 hours of mechanical ventilation support during the ICU stay. Surgery postings were checked manually by one of the authors (L.G.) and divided into surgical type and major vs. minor surgery. Major surgery was defined as open invasive surgery and included surgery via laparotomy, sternotomy, thoracotomy, craniotomy, free flap, and neck dissection. Minor surgery was defined as minimally invasive or superficial surgery, such as laparoscopic, thoracoscopic, endoscopic, and endovascular procedures.

Statistical Analysis

Descriptive statistics were used to examine demographic, clinical, and opioid utilization characteristics of the study cohort. Since the main outcome, mean daily OME use during the ICU course, was skewed to the right, $\log_{10}$ transformation was applied to meet the assumption of normal distribution. Univariable linear regression was conducted to determine the association of each factor with $\log_{10}$(mean daily OME) use in the ICU. The variables with p value of less than 0.15 in the univariable analysis were included in the initial multivariable linear regression model. We then performed backward variable selection, which

excluded the least significant variable in each iteration until the model reached the minimum Bayesian information criterion (BIC). The final multivariable model included the selected variables and four a priori variables kept in the model based on clinical importance (anesthesia duration, at least moderate anxiety, Fibromyalgia Survey Score, and major surgery). Significance was determined by *p* value of less than or equal to 0.05. Since mean daily OME was transformed by $\log_{10}$, the beta estimate should be interpreted as the percentage change in mean daily OME for every one unit increase of a continuous predictor. For dichotomous variables, the beta estimate should be interpreted as the percentage change in mean daily OME when the predictor is present compared with when the predictor is absent. Mathematically, that is, $(10^{\beta}-1) \times 100$, where β is the parameter estimate of the predictor from the model using $\log_{10}$(OME).

Genetic analyses were conducted in participants of European ancestry to avoid confounding by population stratification (30). The SNP or haplotype was coded as 0, 1, and 2 based on the number of minor alleles or haplotypes the individual carried. Univariable linear regression was conducted on each SNP or haplotype with $\log_{10}$(mean daily OME) use in the ICU. The variants with minor allele frequency or haplotypes with frequency threshold less than 0.05 were excluded from analysis. Bonferroni correction was applied to correct for multiple testing. With a total of 19 variants and haplotypes tested, significance was determined by *p* value of less than 0.003.

Analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC) or R 4.3.1 (R Core Team, 2023).

RESULTS

Enrollment

A total of 4195 patients had surgery and an ICU admission between 2012 and 2017. After exclusions outlined in **Figure 1**, the final cohort consisted of 1865 patients.

Demographic and Clinical Characteristics

Mean (SD) age was 56 years (SD, 15 yr), 910 (48.8%) were female, 92.4% were White, 52.3% were ASA class III, and 17 (0.01%) had emergency surgery. Preoperatively, 487 (28.6%) patients were taking prescribed opioids. Participants reported an average of 3.1 (SD, 3.0) of ten on the Brief Pain Inventory Scale, 48.7% had at least moderate anxiety, and 25.9% had at least moderate depression (**Table 1**).

The most common types of surgery were neurosurgery (*n* = 579, 31.0%), cardiac (*n* = 343, 18.4%), otolaryngology/oral maxillofacial (*n* = 194, 10.4%), intra-abdominal (*n* = 174, 9.3%), spine (*n* = 163, 8.7%), interventional radiology (*n* = 70, 3.8%), plastic surgery (*n* = 62, 3.3%), and thoracic (*n* = 35, 1.9%). Most surgeries were classified as major (86.4%). Although surgical case listing and surgical service did not capture whether patients presented due to a trauma, very few

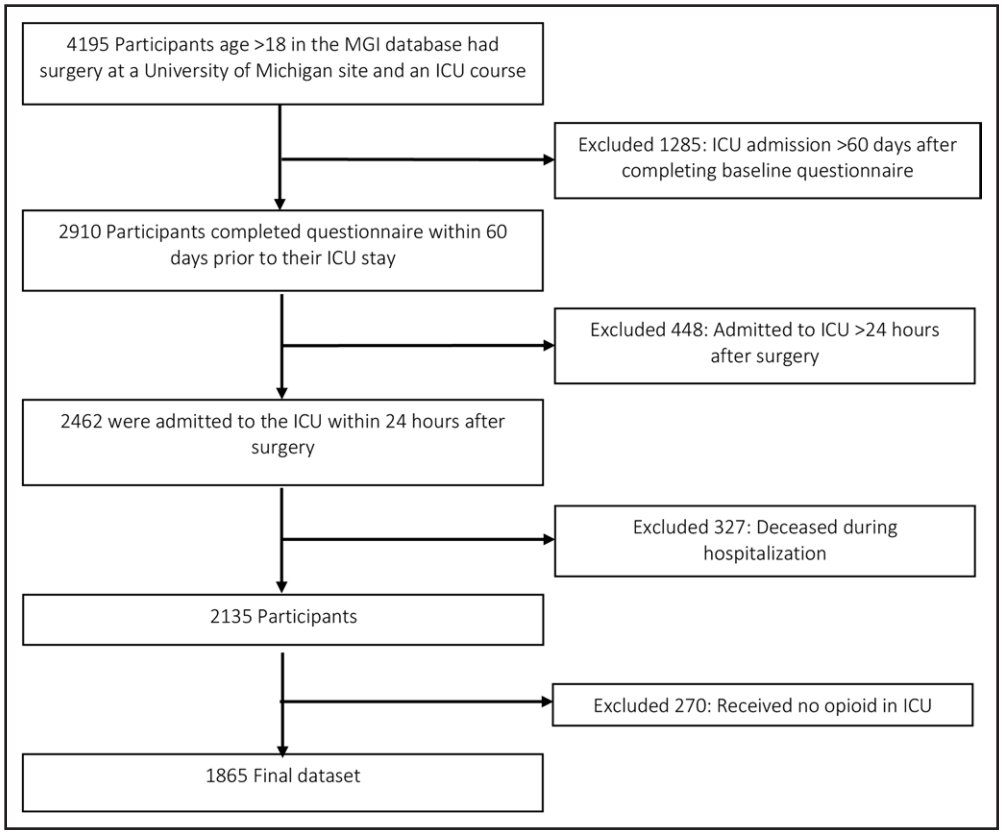

Figure 1. Flow diagram of study enrollment. MGI = Michigan Genomics Initiative.

TABLE 1.
Descriptive and Univariable Analysis of Sociodemographic and Baseline Characteristics and Surgical Factors

Variable (Categorical or Continuous)	Frequency (%) or Mean (SD), *n* = 1865
Age (yr)[a]	56 (15)
Sex	
Female	910 (48.8)
Male	955 (51.2)
Race	
White	1724 (92.4)
African American	84 (4.5)
Other	57 (3.1)
Body mass index[a] (kg/m^2)	30.1 (7.3)
ASA physical status classification	
Class 1	21 (1.3)
Class 2	470 (28.3)
Class 3	870 (52.3)
Class 4	302 (18.2)
Tobacco use	
Current	416 (22.6)
Former	678 (36.8)
Never	751 (40.7)
Alcohol use	
Never	381 (25.7)
Current or former	1102 (74.3)
Illicit drug use	
Never	1604 (92.2)
Current or former	135 (7.8)
Insurance	
Private	843 (57.8)
Medicaid/Medicare	616 (42.2)
At least moderate anxiety	
No	752 (51.3)
Yes	713 (48.7)
At least moderate depression	
No	1081 (74.1)
Yes	378 (25.9)
Life Satisfaction Scale[a]	6.7 (2.7)
Fibromyalgia Survey Score[a]	6.1 (4.8)
Number of chronic pain areas[a]	3.5 (4.4)
Neuropathic Pain Scale[a]	6.6 (7.5)
Brief pain inventory[a]	3.1 (3.0)
Preoperative opioid use	
No	1217 (71.4)
Yes	487 (28.6)
Major surgery	
No	227 (13.6)
Yes	1441 (86.4)
Anesthesia duration (hr)[a]	7.4 (3.0)
> 24 hr ventilator use in ICU	
No	1724 (92.4)
Yes	141 (7.6)

[a]Continuous variable: mean (SD); remaining variables categorical: frequency (%).

cases would be expected given that there were only 17 emergency cases in the cohort. The anesthetic lasted on average 7.4 hours (SD, 3.0 hr), and 7.6% of patients received greater than 24 hours of mechanical ventilation during the ICU course. Mean ICU length of stay was 2.7 days (SD, 3.8 d). Throughout the ICU stay, average OME use per day was 64.3 mg (SD, 106.4 mg).

Opioid Utilization During the Postoperative ICU Encounter

Figure 2 depicts the number of patients who received OME greater than 0 on each ICU-day. Opioid use decreases over the first 4 days postoperatively. The majority of patients receiving opioids in the ICU had undergone major surgery (Fig. 2*A*). Patients who received preoperative opioids were more likely to continue to receive opioids throughout their ICU stay than opioid-naive patients: on day 1, 29% of patients receiving opioids in the ICU had been taking preoperative opioids. By day 10, 57% of patients still receiving opioids in the ICU had been taking preoperative opioids (Fig. 2*B*).

Nonopioid Drugs Utilization During the Postoperative ICU Encounter

Figure 3 depicts nonopioid medications administered over the first 10 days in the ICU. Acetaminophen was

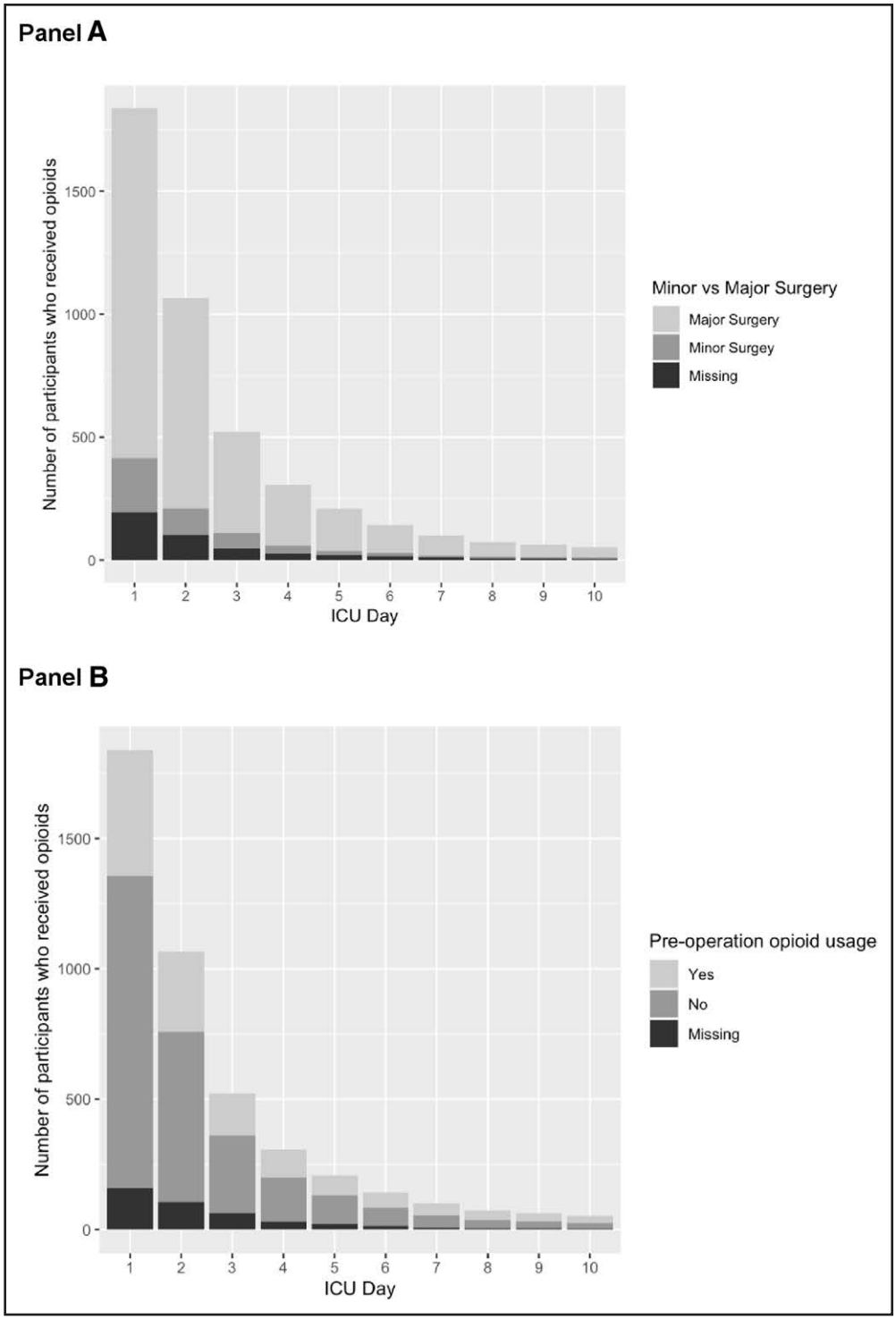

Figure 2. Opioid administration over the first 10 d of the ICU course. **A**, Opioid administration was stratified by major vs. minor surgery. **B**, Opioid administration was stratified by preoperative opioid use.

given on average to 72% of participants every day, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) (38%), and anticonvulsants including gabapentin/pregabalin (24%). The proportion of patients receiving each drug remained relatively constant over time. Propofol was administered to 27% of patients on the first ICU-day and decreased below 10% on subsequent days.

Factors Associated With Opioid Use in the ICU

The initial multivariable regression model for backward variable selection consisted of all variables in Table 1 except sex, age, and body mass index, based on screening criteria of *p* value of less than 0.15 by univariable linear regression. The final model meeting minimum BIC included eight predictors, all of which, except for anxiety, were significantly associated with mean daily OME (**Table 2**). For their effect on mean daily OME use, the parameter estimates were converted back by power of 10: the effect size for age on OME was 0.98, implying that OME decreased by 2% for every 1-year increase in age. Preoperative opioid use increased OME by a factor of 1.67, implying a 67% increase in OME compared with those who did not use preoperative opioids. Current/former drug use increased OME by 30% compared with those who do not use drugs. Preoperative centralized pain increased OME by 3% for every additional point on the Fibromyalgia Survey Score Questionnaire. Anesthesia duration increased OME by 3% for every additional hour of anesthesia.

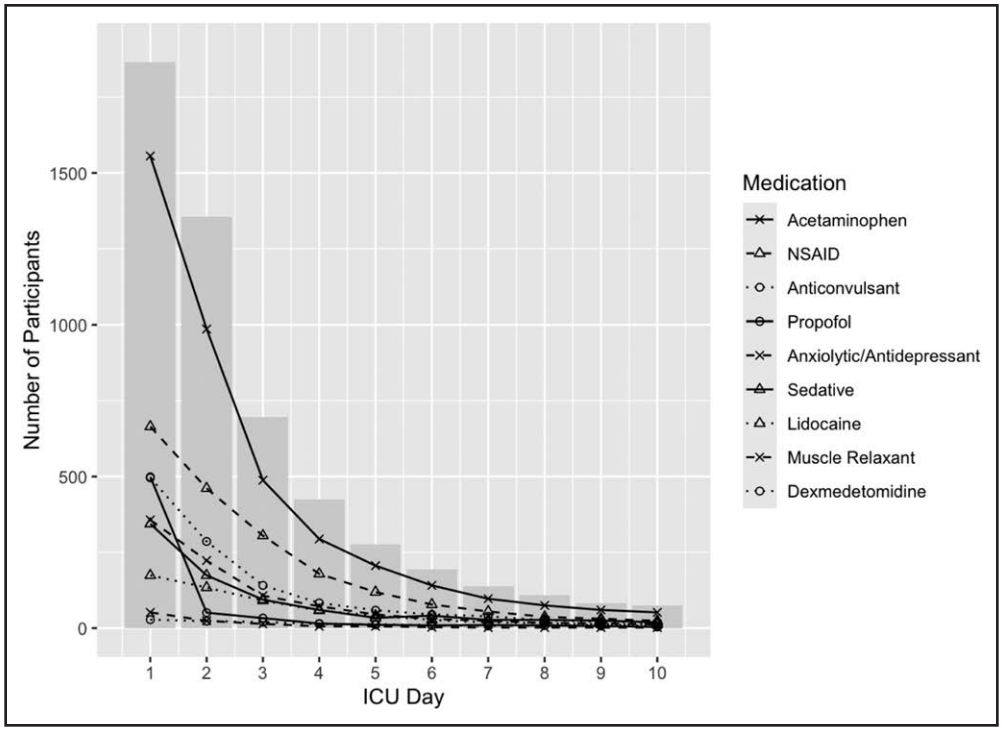

Figure 3. Number of participants receiving nonopioid medications per ICU-day stratified by medication class. *Background bar chart* depicts total number of participants present in the ICU who received postoperative opioids. Anticonvulsants include gabapentin, pregabalin, carbamazepine, and lamotrigine. Anxiolytic/antidepressants include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants. Sedatives include benzodiazepines and diphenhydramine. Muscle relaxants include cyclobenzaprine, baclofen, and tizanidine. Ketamine administration was not depicted because it was administered in less than 1% of participants. NSAID = nonsteroidal anti-inflammatory drug.

Receiving mechanical ventilation greater than 24 hours increased OME by 85% compared with those who did not receive mechanical ventilation. Major surgery increased OME by 62% compared with those who underwent minor surgery.

Genetic Predictors of Opioid Use in the ICU

Genetic analyses were performed in participants of European ancestry (n = 1544) and included SNPs and haplotypes that were known to be associated with pain and/or opioid use (**Table 3**). The allele or haplotype frequency for each variant or haplotype ranged from 6% to 69% (Table 3). Univariable linear regressions to evaluate the association between mean daily OME consumed during the ICU course and genetic variants or haplotypes did not reveal any statistically significant associations. Because the outcome (mean daily OME) was $\log_{10}$ transformed for the analysis, the estimates should be converted back by power of ten to obtain the effect size, as displayed in Table 3.

DISCUSSION

In this large prospective cohort study of patients who were admitted to the ICU after surgery and received postoperative opioids, we found that patients who received preoperative opioids were more likely to continue to receive opioids throughout their ICU stay compared with opioid naive patients. The strongest risk factors of opioid use in the ICU were receiving mechanical ventilation (which increased OME requirements by 85% compared with those not mechanically ventilated), receiving preoperative opioids, and undergoing major surgery. In genetic association analyses of three pain candidate genes, we did not find any statistically significant associations with OME use in the ICU. The strengths of our study included the large cohort size and the availability of detailed baseline preoperative pain and mental/physical characteristics. There has been no study to our knowledge looking at predictors of opioid use during the ICU course specifically. Such genetic analysis in the ICU population has also not been done before.

The experience of pain in the ICU is common (7, 9, 31) and often a traumatic experience (7, 32). Although the treatment of pain is important to improve certain outcomes such as reduce ICU length of stay, duration of mechanical ventilation, and sedation requirements (7, 9), exposure to opioids in the ICU is not without risk. Receiving opioids in the ICU is associated with an increased risk of delirium (33), which in turn can increase cognitive decline (34) and mortality (35). The simple exposure to opioids after a routine procedure can lead to increased odds of continued opioid use (36) and 4% of ICU survivors developed opioid

TABLE 2.

Final Multivariable Linear Regression for Mean Daily Oral Morphine Equivalent Use During the ICU Course With Predictors of Sociodemographic, Baseline Characteristics, and Surgical Factors

Variable	Beta Estimate[a] (95% CI)	*p*	Effect Size[b] (95% CI)
Age (yr)	−0.007 (−0.009 to −0.005)	< 0.0001[c]	0.98 (0.98–0.99)
Current or former illicit drug use	0.12 (0.01–0.23)	0.04[c]	1.30 (1.01–1.68)
Preoperative opioid use	0.22 (0.16–0.29)	< 0.0001[c]	1.67 (1.43–1.96)
At least moderate anxiety	0.02 (−0.04 to 0.08)	0.57	1.04 (0.91–1.19)
Fibromyalgia Survey Score	0.01 (0.007–0.02)	< 0.0001[c]	1.03 (1.02–1.05)
Anesthesia duration (hr)	0.01 (0.002–0.02)	0.02[c]	1.03 (1.00–1.05)
> 24 hr ventilator use in ICU	0.27 (0.15–0.38)	< 0.0001[c]	1.85 (1.41–2.42)
Major surgery	0.21 (0.12–0.30)	< 0.0001[c]	1.62 (1.33–1.97)

[a]Parameter estimates are for $\log_{10}$ transformed oral morphine equivalent (OME).

[b]The effect size for mean daily OME = 10β where β is the beta estimate derived for $\log_{10}$(OME). The effect size value was rounded to two decimal points for reporting purpose. For instance, the effect size of age on mean daily OME implies a 2% decrease in OME for every one-year increase in age. The effect size of preoperative opioid use implies a 67% increase in OME compared with those who did not use preoperative opioids.

[c]Significance determined by $p < 0.05$.

dependence after discharge (6). Risk factors for pain and opioid use vary depending on whether they focus on postsurgical pain or pain after critical illness. Our study, which focused on risk factors during the ICU period specifically, found overlapping risk factors with postsurgical pain (e.g., younger age, preexisting pain, preexisting opioid use, illicit drug use, surgery type, and longer surgery duration) (37–42), and pain after critical illness (e.g., duration of mechanical ventilation) (3). Mechanical ventilation having the largest effect size in our study could perhaps be explained by clinicians having a different threshold for prescribing opioids in mechanically ventilated patients, either as a result of clinical practice guidelines recommending an analgesia-first sedation approach (8), a need for ventilatory synchrony, and/or less concern regarding respiratory depression. The significant influence of mechanical ventilation on ICU opioid use can potentially explain why one particular study, which had a larger proportion of mechanically ventilated patients than in our study, did not find preadmission opioid use as a risk factor for ICU opioid use despite preadmission opioids being associated with worse pain after ICU discharge (43). Furthermore, although psychologic risk factors are important in the development of acute and chronic post-surgical pain (37, 38, 41, 42) and long term after an ICU course (5, 6, 44), psychologic factors did not have a significant impact during the ICU course itself where patients may be sedated and less aware of their surroundings. At the time of patient recruitment for this study, there was no protocol in place in the ICU for the management of pain or administration of opioids. As per routine practice, parenteral opioids are often given postoperatively until patients can transition to oral opioids, and parenteral opioids may be continued for breakthrough pain. A large proportion of patients in our cohort received nonopioid analgesics postoperatively, particularly acetaminophen, NSAIDs, and gabapentinoids. Individual clinician practice variation and judgment, as well as variability in interpreting clinical orders (e.g., how often pain is assessed) is something that is difficult to control and could potentially have had an impact on opioids consumed. Nevertheless, this variability in prescribing and administering opioids may enhance the generalizability of our study.

Genetic factors can also influence one's response to pain. Genetic variations have been shown to explain up to three quarters of the variance in pain responses in animal studies (45). Having a better understanding of genetic risk factors can lead to a more individualized approach to understanding and treating pain. The candidate genes *FKBP5*, *OPRM1*, and *COMT* were chosen based on prior associations with pain: FKBP5 is a key stress response regulator that has led to the

TABLE 3.
Univariable Linear Regression for Associations Between Mean Daily Oral Morphine Equivalent Use During the ICU Course and Genetic Variants or Haplotypes

Gene	Variant[a]	Beta Estimate[b] (95% CI)	p[c]	Allele or Haplotype Frequency[d]	Effect Size (95% CI)[e]
FKBP5	rs3800373 (C)	0.02 (−0.02 to 0.06)	0.74	0.28	1.04 (0.95–1.15)
	rs7753746 (G)	0.02 (−0.04 to 0.07)	0.63	0.16	1.04 (0.92–1.17)
	rs9380526 (C)	0.02 (−0.02 to 0.06)	0.99	0.32	1.04 (0.95–1.14)
	rs9394314 (G)	0.02 (−0.02 to 0.06)	0.98	0.29	1.04 (0.95–1.15)
	rs2817032 (C)	0.02 (−0.02 to 0.06)	0.94	0.27	1.04 (0.95–1.15)
	rs2817040 (A)	0.02 (−0.03 to 0.06)	0.86	0.25	1.04 (0.94–1.15)
OPRM1	rs1799971 (G)	0.02 (−0.04 to 0.07)	0.69	0.13	1.04 (0.91–1.18)
COMT[f]	BLOCK1 (CTA)	0.03 (−0.008 to 0.07)	0.13	0.44	1.07 (0.98–1.16)
	BLOCK1 (CTG)	−0.03 (−0.07 to 0.01)	0.18	0.28	0.94 (0.85–1.03)
	BLOCK1 (TCG)	−0.007 (−0.05 to 0.04)	0.75	0.27	0.98 (0.90–1.08)
	BLOCK2 (CGAG)	0.007 (−0.06 to 0.07)	0.82	0.11	1.02 (0.88–1.18)
	BLOCK2 (CGGG)	0.03 (−0.007 to 0.06)	0.12	0.29	1.07 (0.98–1.16)
	BLOCK2 (TCAA)	−0.03 (−0.07 to 0.007)	0.11	0.24	0.93 (0.85–1.02)
	BLOCK2 (TCGA)	0.001 (−0.07 to 0.07)	0.98	0.08	1.00 (0.85–1.19)
	BLOCK2 (CCGG)	−0.04 (−0.12 to 0.03)	0.25	0.07	0.90 (0.76–1.07)
	BLOCK2 (TCAG)	0.009 (−0.04 to 0.06)	0.72	0.15	1.02 (0.91–1.14)
	BLOCK3 (GA)	−0.02 (−0.06 to 0.03)	0.45	0.69	0.96 (0.88–1.06)
	BLOCK3 (AG)	−0.04 (−0.12 to 0.04)	0.30	0.06	0.91 (0.75–1.09)
	BLOCK3 (GG)	0.03 (−0.01 to 0.07)	0.17	0.25	1.07 (0.97–1.18)

[a]Single nucleotide polymorphism (SNP) (minor allele) or haploblock (haplotype).
[b]Parameter estimates are for $\log_{10}$ transformed oral morphine equivalent (OME). Analysis done in participants of European ancestry ($n = 1544$).
[c]Significance determined by $p < 0.003$ after correction for multiple testing.
[d]Minor allele frequency and haplotype frequency threshold > 0.05.
[e]The effect size for mean daily OME $= 10\beta$ where β is the beta estimate derived for $\log_{10}$(OME).
[f]*COMT* haploblock 1 consists of SNPs rs2020917, rs737865, and rs1544325. *COMT* haploblock 2 consists of SNPs rs4633, rs4818, rs4680, and rs165774. *COMT* haploblock 3 consists of SNPs rs174697 and rs165599.

development of chronic pain and somatic symptoms after traumatic events and persistent pain of neuropathic and inflammatory origin (12, 46); *OPRM1* polymorphism is associated with higher opioid requirements in acute postoperative pain (14); and *COMT* haplotypes are associated with chronic pain after trauma (13). Preexisting factors such as childhood trauma and lower socioeconomic status have been shown to moderate the relationship between *FKBP5* genetic risk factors and chronic pain (47, 48). The interaction of genes with environmental factors is an important consideration for future studies (49, 50) and could explain in part why our findings were not significant. The nature of the pain experienced is also an important consideration. Diatchenko et al (51) found that variations in the *COMT* gene were only associated with sensitivity to certain types of pain (e.g., painful heat stimuli but not mechanical or ischemic pain). This complex nature of pain is also reflected in the fact that preoperative centralized pain was a significant predictor of ICU OME consumption in our study whereas preoperative pain severity from the Brief Pain Inventory was not. With such complex traits such as postsurgical ICU pain, multiple genes are likely simultaneously contributing to pain phenotypes and opioid consumption. Although additional candidate genes could be tested in the ICU population (e.g., *MC1R* can modulate pain sensitivity and μ-opioid

analgesia; *ADRB2* can affect β2-adrenergic receptor signaling; *HTR2A* can affect serotonin receptor signaling; *CYP2D6* can affect the metabolism of opioids; and *SCN9A* encodes a voltage-gated sodium channel subunit, which can affect intracellular neuronal signaling) (15, 45), future studies investigating genome-wide associations with postoperative ICU pain are also needed.

Our findings need to be interpreted in the context of several limitations. This is a single-center study of post-surgical ICU patients, which may not be generalizable to all critically ill patients. Although patient enrollment and the baseline preoperative survey were done prospectively, critically ill patients were identified retrospectively by professional billing codes, and certain datapoints extracted retrospectively could not be obtained with additional granularity (e.g., total preoperative opioid doses). For opioids given in the ICU, we combined all opioids into OME to facilitate analysis instead of analyzing individual opioids given, as is commonly done in the literature (28, 29). Additionally, we did not extract postoperative pain scores since we believed that opioid administration would be titrated to maintain a pain score within the desired range, and we did not extract intraoperative regional/epidural techniques used, as these occurrences were very low. Finally, a vast majority of our population was White, and the genetic analysis was done in patients of European ancestry, which may not be generalizable to other populations.

CONCLUSIONS

In summary, opioid use during a postoperative ICU course is prevalent, and those who were taking preoperative opioids were more likely to continue to receive opioids throughout their ICU stay than opioid-naive patients. Younger age, preoperative opioid use, preoperative centralized pain, illicit drug use, major surgery, longer anesthetic duration, and ICU mechanical ventilation were associated with opioid use during a postoperative critical care course. The selected genetic variants of *FKBP5*, *COMT*, and *OPRM1*, previously shown to be associated with pain outcomes in other settings, were not associated with OME use in this study. Evaluation of the impact of gene-gene interactions, gene-environment moderations on opioid use in the ICU, and genome-wide associations would be important future considerations.

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