



Predictors of Post-operative Pain and Opioid Consumption in Patients Undergoing Liver Surgery

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Abstract

Background Post-operative pain management is a critical component of perioperative care. Patients at risk of poorly controlled post-operative pain may benefit from early measures to optimize pain management. We sought to identify risk factors for post-operative pain and opioid consumption in patients undergoing liver resection.

Methods This is a multi-institutional prospective nested cohort study of patients undergoing open liver resection. Opioid consumption and pain scores were collected following surgery. To estimate the effects of patient factors on opioid consumption (oral morphine equivalents—OME) and on pain scores (NRS-11), we used generalized linear models and multivariable linear regression model, respectively.

Results One hundred and fifty-three patients who underwent open liver resection between 2013 and 2016 were included in the study. The mean patient age was 62.2 years, and 43.3% were female. Younger patients were significantly more likely to use more opioids in the early post-operative period (16.7 OME/10 years, $p < 0.001$). Patient factors that were significantly associated with increased NRS-11 pain scores also included younger patient age (difference in pain score of 0.3/10 years with cough and 0.2/10 years at rest, $p < 0.01$ for both) as well as a history of analgesic use (difference in pain score of 0.9 with cough and 0.6 at rest, $p < 0.01$ and $p = 0.07$, respectively).

Conclusion Younger patients and those with a history of analgesic use are more likely to report higher post-operative pain and require higher doses of opioids. Early identification of these patients, and measures to better manage their pain, may contribute to optimal perioperative care.

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Introduction

Management of post-operative pain is a critical aspect of surgical care. Inadequate post-operative analgesia is associated with increased risks of pulmonary and cardiac complications [1–4]. In the context of an ongoing prescription opioid epidemic, with addiction often resulting from over-prescription of opioids following surgery [5–7], an understanding of risk factors for post-operative pain could aid in judicious, individualized pain management.

Many recent studies of post-operative opioid use have evaluated discharge prescriptions practices, rather than actual inpatient opioid consumption [5, 8–10]. The prescribing practices of physicians are variable and are often subject to provider experience and education, rather than patient needs [5, 10]. While patient factors that are associated with over-prescription of opioids have been identified [5, 9], the impact of patient factors on post-operative pain and actual in-hospital opioid consumption may better reflect the analgesia that patients actually require, rather than the analgesia which patients are prescribed. These measures may allow for early, multimodal analgesic approaches in patients at high risk of post-operative pain or high opioid use.

Open liver resection is a major surgical undertaking with significant post-operative pain. These procedures typically require large subcostal incisions, often with midline extension. Substantial, prolonged retraction of the abdominal wall is often required to reach right-sided and posterior liver segments. Identification of risk factors for increased post-operative pain and for increased opioid consumption in patients undergoing open liver resection may allow for early identification and early intervention to manage post-operative pain. The purpose of this study was to identify such risk factors.

Methods

Study setting and design

This study was performed as a secondary analysis to a multicenter randomized controlled trial of surgeon-placed medial open transversus abdominis plane (MOTAP) catheters [11, 12]. This trial was carried out at two high-volume hepatobiliary centers in Toronto, Canada. All enrolled patients underwent open liver resection through a right subcostal incision and received MOTAP catheters using a standardized method. Patients were randomized 1:1 to receive either 0.2% ropivacaine (ROP—experimental group) or 0.9% normal saline (NS—control group) through their MOTAP catheter. Catheters were kept in place and

managed by the Acute Pain Service (anesthesia) at each hospital for 3 days post-operatively.

All patients in the trial were given intravenous patient-controlled analgesia (IV-PCA), which administered hydromorphone, in addition to oral celecoxib. Post-operative opioid consumption was recorded every 12 h for the first 72 h after surgery, and post-operative pain scores were recorded three times daily following surgery.

We performed analyses on the data from this trial to evaluate the association between patient-level variables and opioid use and pain while adjusting for the study arm to which patients were assigned. The randomized controlled trial and all secondary analyses were approved by the research ethics boards of Sunnybrook Health Sciences Centre and Toronto General Hospital.

Outcomes

The primary outcome for this study was total opioid use at 72 h. Opioid use was recorded as oral morphine equivalents (OME). The primary opioid used was hydromorphone which was converted to OME at a scale of 1:4. As secondary outcomes, we also evaluated post-operative pain. Pain intensity was recorded using patients' self-report of the Numeric Rating Scale (NRS-11) in which pain was rated by patients with the assistance of a visual aid on a scale from 0 to 10, with 0 being no pain at all. Pain scores at rest and with coughing were compared as continuous outcomes across all time points. We also evaluated pain scores as dichotomized variables—either “No pain or mild pain” (for those reporting pain scores of 0–3) or “Moderate or greater pain” (for those reporting pain scores of 4 or greater) on post-operative day 2 (POD2).

Covariates

We evaluated patient-level variables that may be predictive of post-operative opioid use and pain scores. These variables included patient age, sex, body mass index (BMI), and preoperative analgesic use. Patients were asked to complete a preoperative questionnaire, which included items regarding previous analgesic use. Patients were asked whether they were currently taking any medications for pain, including aspirin, acetaminophen, NSAIDs, opioids (short-term), or others. For the purposes of this study, analgesic use was treated as a dichotomous variable (yes/no). Patients with a history of chronic pain or chronic opioid use as determined by an anesthesiologist were excluded from the study.

Analysis

We performed descriptive statistics to evaluate baseline characteristics of the cohort. We performed univariate analyses to evaluate the relationship between patient factors and opioid use at 72 h. For categorical variables, we performed Wilcoxon rank-sum tests to compare the median opioid consumption across categories. For continuous variables, we performed linear regressions to estimate the association between individual patient-level variables and opioid consumption. We then used a multivariable linear regression to evaluate the adjusted impact of patient factors on opioid consumption. Included in the multivariable model were a priori selected patient variables described above (age, sex, BMI, and preoperative analgesic use) as well as the study arm to which patients had been randomized.

Assumptions for the linear regression model were tested. We tested for influential outliers, which were excluded from analysis ($n = 2$), and we ensured normal distribution of residuals prior to proceeding with the model.

We performed univariate analysis of pain scores on POD2. For this analysis, pain was then treated as a dichotomous outcome with patients either having “No pain or mild pain” (NRS 0–3) or “Moderate or greater pain” (NRS-11 ≥ 4). Univariate analysis was performed using Chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. We then used generalized linear equations using maximum likelihood estimation to model the association between patient-level factors and pain scores across all time points while accounting for the clustered nature of repeated measures. Covariates for these models included the a priori selected patient factors described above as well as the study arm.

Given the prospective nature of data collection, we expected a low incidence of missing data and complete case analysis was performed. All statistics were performed using SAS software version 9.2 (SAS Inc, Cary, NC). All tests were two-sided, and significance was considered at $p < 0.05$.

Results

After screening, consent, and randomization, 153 patients were included in the randomized controlled trial. All patients who were included in the randomized controlled trial were included in the secondary analysis. The mean patient age was 62.2 years (SD 12.1), and 43.3% were female (Table 1).

Approximately 51% of procedures were recorded as “Other” by the surgical team, reflecting a prevalence of non-anatomic liver resections. Among procedures that

Table 1 Baseline demographics of study patients

	All patients ($n = 153$)
Age (median, IQR)	63 (54–71)
Sex (female)	63 (41.3%)
Analgesic use	22 (14.4%)
Diagnosis	
Colorectal liver metastases	92 (59.3%)
Hepatocellular carcinoma	21 (13.7%)
Intrahepatic cholangiocarcinoma	14 (9.2%)
Gallbladder adenocarcinoma	13 (8.5%)
Other	13 (8.5%)
Procedure	
Right hepatectomy	36 (23.5%)
Bisegmentectomy	9 (5.8%)
Left hepatectomy	8 (5.2%)
Right posterior sectionectomy	8 (5.2%)
Left lateral sectionectomy	6 (3.9%)
Right trisectionectomy	3 (2.0%)
Left trisectionectomy	2 (1.3%)
Right anterior sectionectomy	2 (1.3%)
Other (non-anatomic resection or combination)	79 (51.6%)

involved conventional anatomical resections, right hepatectomy was the most common procedure, followed by bisegmentectomy and left hepatectomy.

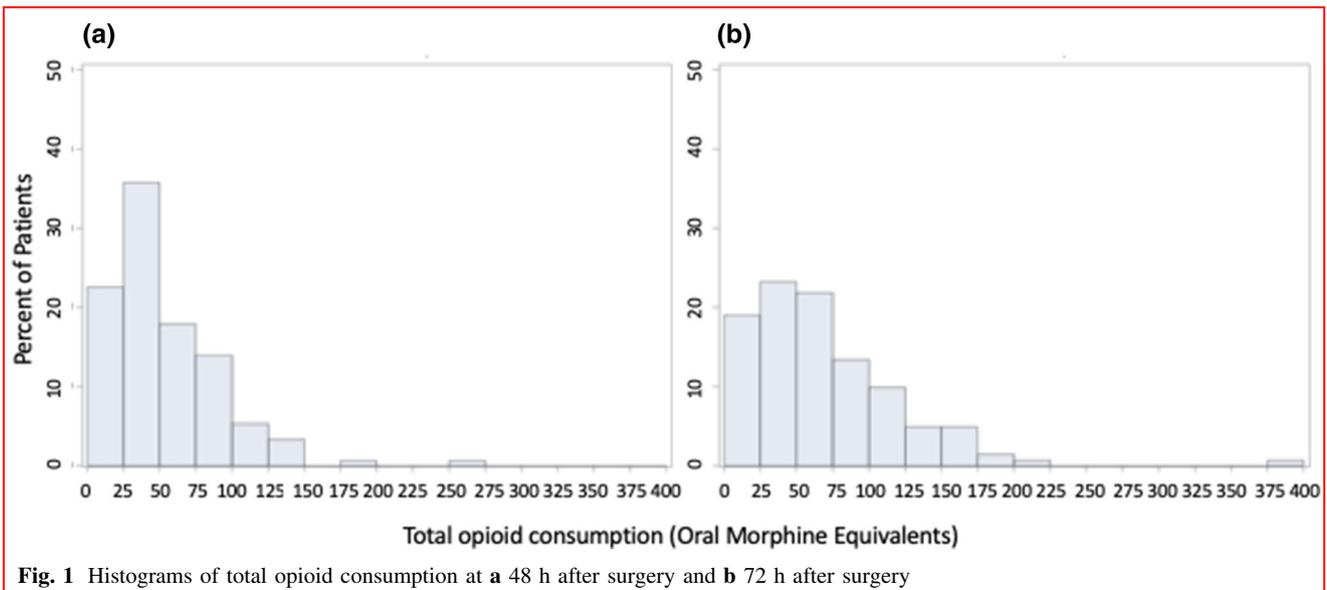
All patients underwent an open liver resection with subcostal incision and placement of a MOTAP catheter. Seventy-one patients were randomized to the experimental group and received ROP through their MOTAP catheter, and 82 patients were randomized to the control group and received NS through their MOTAP catheter.

Data regarding all baseline characteristics, study arm allocation, and opioid consumption were complete for all patients. Post-operative pain scores for POD2 were missing for eight patients.

Opioid use

Post-operative opioid use varied widely among patients undergoing open liver resection. Across the entire cohort, the inter-quartile range of opioid use at 72 h was 31.2–96.0. Ten percentage of the cohort used 20 or less OME of opioids, while 10% used more than 130 OME. Figure 1 shows the distribution of opioid use across all patients at 48 h after surgery and at 72 h after surgery.

Considerable variability was also found after dividing the cohort into subgroups based on the study arm. Among patients in the experimental (ROP) arm, the inter-quartile



range of opioid use at 72 h was 29–80 OME. Among those in the control (NS) arm, the inter-quartile range of opioid use at 72 h was 34–111 OME.

For all patients, the median opioid consumption at 72 h was 56.2 OME (IQR: 31.2–96.0). On univariate analysis, there was no significant association between opioid consumption at 72 h and patient gender ($p = 0.377$). Patients with current analgesic use had a median opioid consumption of 74.8 OME (IQR: 21.6–116.0) compared to 54.4 OME (32.0–92.4) among those without analgesic use, although the number of patients with current analgesic use was relatively small ($n = 22$, 14% of cohort), and the study was not sufficiently powered for this difference to be statistically significant ($p = 0.37$). Opioid consumption at 72 h was significantly associated with younger patient age ($\beta = -1.88$, $p < 0.0001$) and greater BMI ($\beta = 1.84$, $p = 0.049$).

We also stratified patient age into five groups and performed Wilcoxon rank-sum tests to evaluate the association between age-group and opioid consumption. Patients in the youngest age-group (younger than 40 years) consumed fourfold more opioids in the first 72 h following surgery than patients in the oldest group (older than 70 years) ($p < 0.0001$, Fig. 2).

After adjusting for patient factors as well as study arm, younger patient age was significantly associated with greater opioid consumption at 72 h ($\beta = -1.67/\text{year}$, $p < 0.0001$), suggesting that for every 10 years younger than the mean, opioid consumption increases by approximately 17 OME. Female sex also had a large effect size on opioid use, trending toward lower opioid use, which approached statistical significance ($\beta = -12.4$, $p = 0.087$) (Table 2). The R-squared statistic of this model was 0.23,

suggesting that 23% of variability in opioid use between patients may be explained by these factors.

Post-operative pain scores

Pain scores decreased over the course of the post-operative period. The proportion of patients reporting “Moderate or greater pain” (NRS-11 score ≥ 4) at rest and with coughing decreased steadily over post-operatively, with pain scores while coughing being greater than those at rest at all time points (Fig. 3).

On univariate analysis, there was a trend toward lower median pain scores with increased patient age on POD2 that approached statistical significance ($p = 0.054$ between the youngest and oldest groups) (Fig. 4). When we dichotomized pain scores to either “Moderate or greater” or less, there was no significant association between patient sex, BMI, or age and having moderate or greater pain on POD2 ($p > 0.05$ for all). Patients with analgesic use were significantly more likely to experience moderate or greater pain at rest (31.8% vs 14.5%, $p = 0.045$) (Fig. 5).

We used generalized linear models to estimate the association between patient-level covariates and post-operative pain across all time points following surgery while adjusting for the study arm to which patients were assigned. For pain with cough, younger patient age ($\beta = -0.03/\text{year}$, $p = 0.003$) and analgesic use ($\beta = 0.92$, $p = 0.006$) were both significantly associated with greater pain score. For pain at rest, younger age was again significantly associated with greater post-operative pain score ($\beta = -0.023/\text{year}$, $p = 0.013$) and analgesic use approached, but did not reach statistical significance ($\beta = 0.56$, $p = 0.07$) (Table 3). We also used multivariable logistic

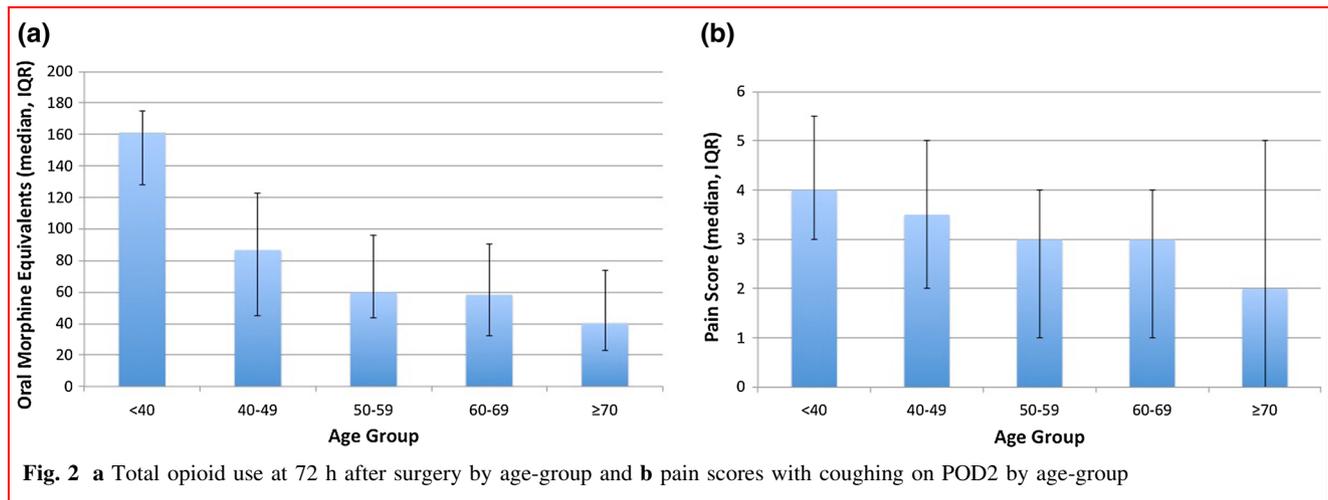


Table 2 Linear regression for total opioid use at 72 h after surgery

Predictor	Adjusted beta coefficient	<i>p</i> value
Age (per year)	− 1.67	< 0.0001
Sex (female)	− 12.41	0.087
BMI	− 0.02	0.978
Analgesic use	11.09	0.278
Study arm (ROP)	− 15.80	0.023

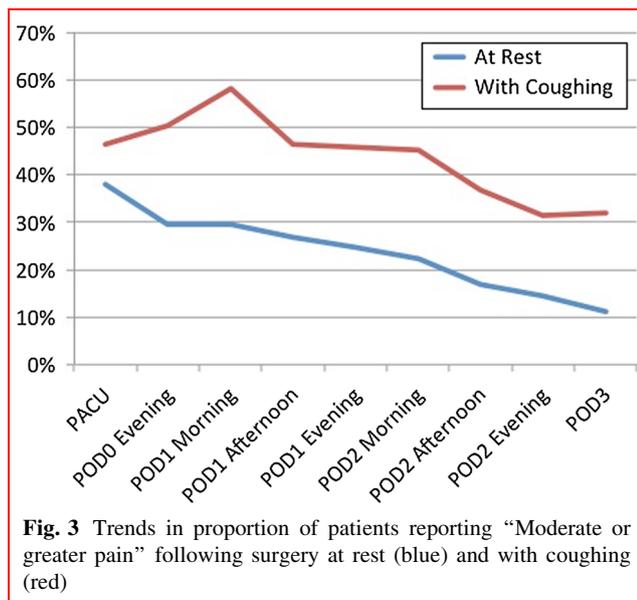
between female sex and post-operative pain approached, but did not reach, statistical significance (OR 2.1, 95%CI 0.84–5.29, *p* = 0.10). The model had a good fit (Hosmer and Lemeshow goodness of fit: *p* = 0.78) and an area under the curve (AUC) of 0.77.

Discussion

In this study of post-operative opioid use and pain scores among patients undergoing open liver resection, patient factors that were significantly associated with either increased post-operative opioid use score or greater pain score included younger patient age and preoperative analgesic use.

In our cohort, after adjusting for covariates, for every 10 years of age younger than the mean age (62 years), patients required approximately 17 OME more opioids at 72 h. Considering the median opioid consumption at 72 h was 56 OME, this represents an increase of approximately 30%.

An understanding of patient factors that may be associated with poor post-operative pain control and/or high opioid consumption may allow for a number of interventions in these patients that could mitigate excessive in-hospital opioid use as well as post-discharge over-prescription. Patients may benefit from early involvement of a dedicated pain service, the use of multimodal analgesic approaches to limit opioid use, as well as adjunct dosing of non-opioid analgesics and closer post-operative monitoring of pain. Combined use of IV-PCA and either transversus abdominis plane (TAP) blocks (placed either by the surgeon intraoperatively or by an anesthesiologist perioperatively) or thoracic epidurals is the example of commonly used multimodal approaches that may be used in patients at risk of high post-operative opioid use. At our own institutions, routine involvement of an Acute Pain Service to



regression to estimate the odds of reporting moderate or greater pain on POD2 while adjusting for patient factors and study arm. The only covariate that was significantly associated with moderate or greater pain was analgesic use (OR 3.4, 95%CI 1.09–10.62) (Table 4). The association

Fig. 4 Pain scores with coughing on POD2 by age-group

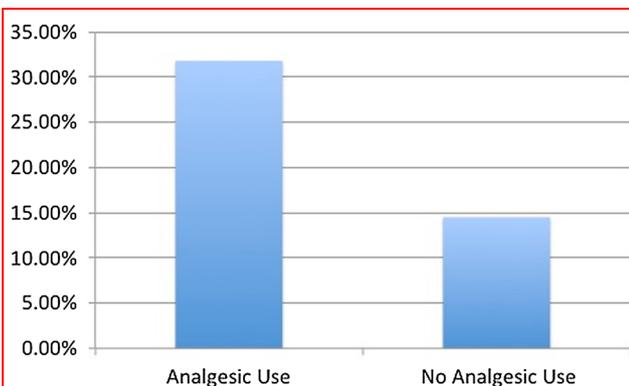
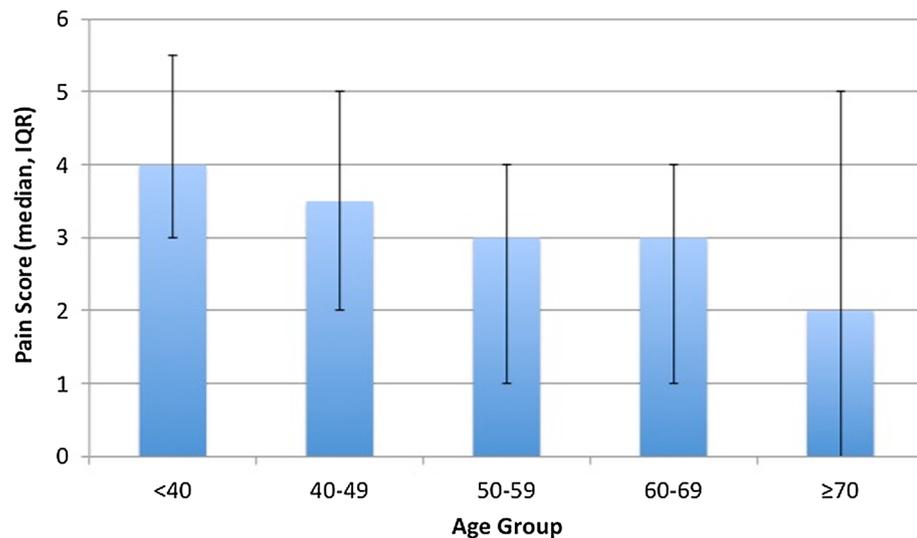


Fig. 5 Proportion of patients reporting “Moderate or greater pain” at rest on POD2

manage post-operative pain through a multimodal analgesic approach has been implemented to streamline pain management and reduce opioid use. Preoperative assess-

ments by anesthesia services help to identify patients who may have challenging post-operative pain management.

Several large studies have evaluated practices regarding the prescription of opioids on discharge following surgery and have demonstrated predictors of over-prescription [5, 9]. These studies have identified wide variability between practitioners prescribing practices and patients' post-discharge opioid needs, often measured in a number of refills. In general, most studies have found a disconnect between prescribing practices and patient needs, often resulting in over-prescription [5, 13]. Many patients do not use all of their prescribed opioids, and there has been a push in recent years to reduce the quantity of opioids prescribed across many common surgical procedures [10]. However, an understanding of the patient-level variability in the experience of pain and in opioid consumption could assist practitioners in prescribing the right amount of opioids for the right patients. Our study identifies two easily identifiable factors that may facilitate a more individualized approach to post-operative analgesia.

Table 3 Generalized linear model for pain with coughing and pain at rest across all time points

Predictor	Pain with coughing		Pain at rest	
	Adjusted beta coefficient	<i>p</i> value	Adjusted beta coefficient	<i>p</i> value
Age (per year)	− 0.03	0.003	− 0.023	0.013
Sex (female)	0.04	0.875	0.21	0.342
BMI	0.01	0.657	− 0.01	0.644
Analgesic use	0.92	0.006	0.56	0.070
Study arm (ROP)	− 0.74	0.002	− 0.66	0.002

Table 4 Logistic regression for moderate or greater pain at rest (POD2 afternoon)

Predictor	Odds ratio	95% Confidence interval
Age (per year)	1.01	0.97–1.05
Sex (female)	2.14	0.87–5.26
BMI	1.08	0.98–1.18
Analgesic use	4.24	1.40–12.83
Study arm (ROP)	0.31	0.12–0.80

The findings of our study are supported by the existing literature of post-operative pain. The previous studies have found a similar inverse association between patient age and post-operative pain and opioid requirements [14–18]. Patient-reported preoperative analgesic use, which was significantly associated with greater post-operative pain in our study, has not been well described as a predictive factor in the existing literature. Analgesic use may serve as an easily identifiable preoperative risk factor to help optimize post-operative analgesia.

While the link between over-prescription of opioids at discharge and long-term opioid use has been well demonstrated in several large studies [6, 8, 9, 19, 20], the impact of in-hospital opioid consumption has not been well studied. Opioid prescription varies between practitioners and between patients [5], and it is likely that in-hospital opioid use and pain are significant factors in prescribing practices. Existing evidence suggests that a preventive multimodal approach to postsurgical analgesia may reduce the risk of chronic postsurgical pain [21]. Early identification of patients likely to experience high post-operative pain and opioid use may facilitate early interventions to mitigate reactionary opioid over-prescription.

Furthermore, current opioid prescription practices may not accurately reflect patient needs. In a study of prescribing practices of 7651 patients undergoing 25 common surgical procedures identified using the National Surgical Quality Improvement Program (NSQIP), higher doses of opioids tended to be prescribed to older patients (median 375 OME in patients younger than 40 years vs 425 OME in patients older than 80 years, $p < 0.001$) and female patients (390 OME vs 375 OME in males, $p = 0.002$) [5]. The data from our study suggest that older patients are less likely to report high post-operative pain scores and are likely to use less post-operative opioids. While underpowered, our results also suggested that female patients might in fact require less post-operative opioids.

Our study benefited from the randomized controlled trial design, which facilitated rigorous, prospective data collection. Our study also benefited from relative homogeneity in surgical approach allowing us to compare pain and

opioid use across patients with minimal differences being attributable to procedure. All patients included in the study underwent similar procedures with regard to factors that may be associated with post-operative pain—patients had similar surgical incisions (open, subcostal) and similar abdominal wall retraction.

One limitation of this study is the generalizability to other surgical procedures or other surgical populations. While the homogeneity of the cohort contributed to internal validity, it likely limited the external validity of our findings. The covariates that we included in our model were not an exhaustive list, and important patient-level factors were likely unaccounted for; in particular, we were not able to include the type of preoperative analgesics that patients used in our models. Moreover, post-operative pain is an individual and widely variable experience that involves surgical, psychosocial, environmental, and genetic factors [21], and attempts to predict pain or opioid use should be mindful of the limitations in doing so.

Considerable work remains in optimizing post-operative analgesia and mitigating the risks associated with opioid use. Future studies should explore the link between in-hospital opioid consumption and over-prescription at the time of discharge. Additionally, further work to explore predictors of high post-operative pain and high opioid use will be important additions to the literature.

Conclusion

Younger patients and those reporting any analgesic use are significantly more likely to report higher post-operative pain and have increased inpatient opioid consumption. Patients with these risk factors may benefit from early intervention to better manage surgical pain.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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