Predictors of In-Hospital Opioid Consumption and Discharge Prescribing Following Caesarean Delivery

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DEDICATION

This thesis is dedicated to my Queer community. I am so glad I found you. I will take everything I learned writing this thesis and use it to serve, support, and uplift our community to ensure we can all live as we truly are.

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ABSTRACT

Background: Opioids are widely prescribed for postoperative analgesia after caesarean delivery (CD), however, increased postoperative opioid consumption may lead to adverse events that hinder recovery (i.e., postoperative nausea and vomiting, and dependence). To enhance the quality of care after CD, it is essential to understand patients' current in-hospital analgesia requirements, as well as identify modifiable factors associated with increased opioid consumption and prescription at discharge.

Objective: The primary aim of this study was to assess the rates and predictors of in-hospital opioid consumption following CD. Secondarily, we compared 30-day postoperative outcomes among opioid consumers versus non-consumers and assessed the rates and predictors of opioid prescription at hospital discharge following CD.

Methods: This retrospective cohort study included patients undergoing CD under neuraxial anesthesia at a university-affiliated hospital from 12/2020-12/2021. Patient demographics, care characteristics, in-hospital opioid consumption and discharge prescription (converted to the equivalent number of morphine 5 mg pills) were collected from medical records. Predictors were analyzed using negative binomial regression with missing data addressed using multiple imputations.

Results: A total of 904 patients were included (age 34.9±5 years, gestational age 38±3 weeks, multiple gestations 5%, previous CD 44%, emergency CD 40%, length of stay 2.3±1.1 days). In-hospital analgesia prescriptions included acetaminophen (100%), nonsteroidal anti-inflammatory drugs [NSAIDs] (91%), and opioids (100%). Only 45.5% of patients consumed opioids in-hospital (median consumption = zero [IQR 0-2] morphine 5 mg pills; mean = 1.9±8.1 pills). Increased opioid consumption was associated with opioid use during pregnancy (vs. none)

(Incidence Rate Ratio [IRR] 9.419 [95%CI 3.425-25.900]), higher postoperative pain scores in-hospital (1.599 [95%CI 1.524-1.678)], and higher post-anesthesia care unit opioid consumption (1.007 [95%CI 1.002-1.013]), while decreased opioid consumption was associated with NSAIDs consumption (0.613 [95%CI 0.460-0.818]). In-hospital opioid consumption (vs. no consumption) was significantly associated with longer length of stay (2.4±1.0 days vs. 2.1±0.5 days, $p<0.001$), and higher incidences of in-hospital postoperative nausea and vomiting (28.1% vs. 19.6%, $p=0.003$), 30-day postoperative complications (13.2% vs. 7.1%, $p=0.002$), and hospital readmissions (2.4% vs. 0.6%, $p=0.025$). At discharge, 89% of patients were prescribed opioids (median of 20 morphine 5 mg pills [IQR 20-20]; mean 17.5±8.3 pills). Decreased opioid prescription at discharge was associated with receiving a pre-printed discharge prescription with a lower number of morphine 5 mg pills (ten vs. twenty; 0.548 [95%CI 0.389-0.770]).

Conclusions: This study supports that in-hospital opioid consumption following CD is generally low, with certain patient and care factors associated with increased opioid use. The consumption of opioids was associated with longer length of stay, and increased risk of nausea and vomiting, postoperative complications, and hospital readmissions. At discharge, the use of preprinted prescriptions was the sole factor associated with the quantity of opioids prescribed. These findings can inform strategies to mitigate opioid-related harms following CD.

RÉSUMÉ

Introduction: Les opioïdes sont fréquemment prescrits après les césariennes. Cependant, la consommation élevée d'analgésiques opioïdes à l'hôpital peut causer des effets secondaires qui retardent le rétablissement (ex. la nausée, les vomissements, la dépendance). Afin d'améliorer la qualité de soins après les césariennes, il est nécessaire de comprendre les demandes analgésiques des patients et identifier des facteurs de risques modifiables associés à la consommation d'opioïdes.

Objectif: L'objectif principal de cette étude était d'évaluer les taux et prédicteurs de la consommation des opioïdes après les césariennes. Les objectifs secondaires étaient de comparer les résultats postopératoires jusqu'à 30 jours après la chirurgie entre les patients ayant consommé des opioïdes les patients qui n'en consommaient pas, ainsi que d'évaluer les taux et prédicteurs de prescription d'opioïdes à la sortie de l'hôpital.

Méthodes: Cette étude d'une cohorte rétrospective inclut des patients ayant subi une césarienne sous l'anesthésie neuraxiale dans un hôpital universitaire entre 12/2020-12/2021. L'information démographique, les détails de la chirurgie, la consommation d'opioïdes à l'hôpital et les ordonnances de sortie (en nombre de comprimés de morphine à 5 mg) ont été collecté des dossiers médicaux. Des modèles de régression binomiale négative ont été utilisés pour évaluer l'association de la consommation et la prescription d'opioïdes avec les prédicteurs potentiels. L'imputation multiple a été utilisée pour traiter les données manquantes.

Résultats: 904 patients ont été inclus (âge moyen 34,9±5 ans, âge gestationnel 38±3 semaines, grossesses multiples 5%, césarienne antérieure 44%, césarienne d'urgence 40%, durée du séjour à l'hôpital 2,3±1,1 jour). À l'hôpital, les patients ont été prescrits l'acétaminophène (100%), d'anti-inflammatoires non stéroïdiens [AINS] (91%) et des opioïdes (100%). Seulement 45.5%

des patients consommaient des opioïdes à l'hôpital (consommation médiane = zéro [écart interquartile (EI) 0-2] comprimés de morphine 5 mg; moyen = 1.9±8.1 comprimés). La consommation d'opioïdes élevée à l'hôpital a été prédite par la consommation d'opioïdes pendant la grossesse (rapport des taux d'incidence 9,419 [95%CI 3,425-25,900]), des scores de douleur postopératoire élevés à l'hôpital (1,599 [95%CI 1,524-1,678]) et la consommation d'opioïdes plus élevée dans la salle de réveil (1,007 [95%CI 1,002-1,013]). La consommation d'opioïdes réduite a été prédite par la consommation d'AINS à l'hôpital (0,613 [95%CI 0,460-0,818]). Les patients ayant consommé des opioïdes à l'hôpital avaient une durée de séjour plus longue (2,4±1,0 jours vs. 2,1±0,5 jours, p<0,001) et présentaient des taux de nausées et de vomissements (28,1% vs. 19,6%, p=0,003), de complications chirurgicales jusqu'à 30 jours après la chirurgie (13,2% vs. 7,1%, p=0,002) et de réadmission à l'hôpital (2,4% vs. 0,6%, p=0,025) plus élevés que les patients qui n'en consommaient pas. À leur sortie, 89% des patients ont reçu une prescription d'opioïdes (médiane = 20 comprimés de morphine 5 mg [EI 20-20]; moyen = 17,5±8,3 comprimés). Une quantité réduite d'opioïdes prescrite a été associée à un formulaire de prescription de sortie préimprimé contenant dix comprimés de morphine 5 mg au lieu de vingt (0,548 [95%CI 0,389-0,770]).

Conclusion: Selon cette étude, la consommation d'opioïdes après les césariennes est basse. Nous avons identifié des prédicteurs de la consommation d'opioïdes liés aux patients et aux procédures. Les patients qui consomment des opioïdes avaient une durée de séjour plus longue et étaient plus susceptibles aux nausées et vomissements, de complications chirurgicales, et de réadmission à l'hôpital. La quantité d'opioïdes prescrite a été prédite seulement par le formulaire de prescription préimprimé. Ces résultats peuvent éclairer des stratégies pour réduire les effets nocifs des opioïdes après les césariennes.

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PREFACE AND CONTRIBUTION OF AUTHORS

This manuscript-based thesis reports the following study:

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Dr Raman Agnihotram

Supervised data analysis and contributed to manuscript revision.

Dr Liane Feldman

Contributed to study design, supervised data collection, analysis, and interpretation, and reviewed all drafts of the manuscript.

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

CD: Caesarean Delivery

ERAS: Enhanced Recovery After Surgery

PROSPECT: Procedure Specific Postoperative Pain Management

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs

CNS: Central Nervous System

IQR: Interquartile Range

IRR: Incidence Rate Ratio

PACU: Post-Anesthesia Care Unit

STROBE: Strengthening the Reporting of Observational studies in Epidemiology

MUHC: McGill University Health Centre

REB: Research Ethics Board

POD: Postoperative Day

ASA: American Society of Anesthesiologists

EMR: Electronic Medical Records

MME: Morphine Milligram Equivalents

PONV: Postoperative Nausea and Vomiting

USA: United States of America

SD: Standard Deviation

PPROM: Preterm Premature Rupture of Membranes

HELLP: Hemolysis Elevated Liver Enzymes and Low Platelets

EPDS: Edinburgh Postnatal Depression Scale

PO: “Per Os” oral medication

IV: Intravenous

SC: Subcutaneous

PR: Per Rectum

PRN: “Pro Re Nata” as needed

WHO: World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Caesarean delivery

Caesarean delivery (CD) is the most commonly performed major surgery worldwide.[1,2] Globally, CD is estimated to account for 21% of all births and is expected to reach 29% in 2030.[3] Indications for CD include fetal distress, pregnancy complications, fetal malpresentation, and prolonged or arrested labour.[3] The increasing incidence of CD is suggested to result from a combination of clinical and socio-cultural factors, such as increasing rates of advanced maternal age, obesity, and a rise in CD performed for non-medical reasons (e.g., maternal and/or clinician preference).[4,5]

Although CD has saved the lives of countless patients and infants, this procedure is not without significant risks. Several studies support that over half of CD patients experience moderate-to-severe postoperative pain. [6-8] Also, compared to vaginal delivery, CD is associated with increased risk of postpartum complications such as hemorrhage, infection, thromboembolism, and endometriosis.[9,10,11] Long-term risks for CD patients include chronic postpartum pain,[12] as well as increased risk of complications in subsequent pregnancies compared to patients undergoing vaginal delivery.[13] For infants, CD is also associated with long-term risks, including increased rates of immune,[14] metabolic,[15] and respiratory diseases.[16] Given the overwhelming and increasing number of patients who undergo CD, there is an urgent need to mitigate the risks associated with this procedure and improve outcomes.

1.2 Postoperative analgesia for caesarean delivery

Ensuring effective postoperative pain management following CD is crucial for enhancing both patient and infant outcomes. Unlike other surgical populations, patients undergoing CD have the

added challenge of caring for a newborn postoperatively. Unsurprisingly, postoperative pain impacts their ability to bond with, care for, and feed their newborns.[17,18] In qualitative studies, CD patients have expressed difficulties caring for newborns as a result of their pain.[19] While patients undergoing CD already have lower rates of breastfeeding than patients undergoing vaginal delivery,[20] poorly managed postoperative pain can exacerbate this issue.[21] Furthermore, poor postoperative pain management is associated with increased rates of chronic pain and postpartum depression.[22,23] Given these significant implications, achieving adequate postoperative analgesia that takes into account the unique needs of CD patients must be a priority to enhance the quality of postpartum care.

Intraoperatively, neuraxial anaesthesia with intrathecal or epidural morphine is considered the gold standard pain management intervention during CD. [24-26] This approach provides lasting analgesia for several hours postoperatively. [24-26] Additional analgesia interventions that may be performed in the operating room include peripheral nerve blocks,[27] fascial plane blocks,[28] and wound infusions with local analgesics.[29,30] The use of epidural analgesia beyond the operating room is becoming less frequent used due to the barriers it presents to early postoperative mobilization[31,32] and its association with urine retention[31,33] and longer length of hospital stay.[24,34] Currently, the Enhanced Recovery After Surgery (ERAS) Society[24] and the PROSPECT Working Group[25] recommend the use of oral multimodal postoperative analgesia after CD, including non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen with rescue opioids for breakthrough pain.

1.3 Opioid analgesia

Opioids have been used for their analgesic properties for thousands of years,[35] and remain a cornerstone for the treatment of perioperative,[36] chronic,[37] and cancer pain.[38] Opioids act by

binding to mu-, delta-, and kappa-opioid receptors in the central nervous system (CNS) and peripheral tissues.[39,40] They impact the detection and propagation of pain signals through multiple mechanisms, such as by activating inhibitory descending pathways in the CNS[41] and directly inhibiting ascending pain signals in the periphery.[35,42] The potential for opioid misuse stems from their activation of the reward systems of the brain, resulting in the release of dopamine in the nucleus accumbens and contributing to feelings of euphoria.[43,44] Through repeated exposures, neurons' levels of activity adjust, producing withdrawal symptoms when opioids are not present in the body and contributing to opioid dependence.[44] In addition to physical dependence, repeated administration of opioids may result in desensitization to their analgesic effects and the development of opioid-induced hyperalgesia.[45] Studies performed by Guignard et al. (2000)[46] and Chia et al. (1999)[47] support that opioid consumption during the intraoperative and postoperative periods can increase opioid tolerance and pain sensitivity.

Opioids are widely prescribed in North America for postoperative analgesia following CD, however, these drugs present potential risks to patients and their infants.[48-50] The presence of opioid receptors in a wide variety of tissues and organs contributes to the diverse range of side effects associated with these drugs, including nausea, vomiting, constipation, and sedation.[51,52] These adverse events can hinder recovery following CD and are of concern to patients.[53] Notably, a cross-sectional study indicated that after pain, vomiting and nausea were the least desired anesthesia outcomes following CD.[53] Furthermore, opioids may also present risks for the breastfeeding infants of CD patients, such as central nervous system and respiratory depression.[54-59] Opioid-related adverse events are also associated with significant increases in healthcare costs and length of hospital stay in obstetrics patients.[60] As many opioid-related adverse events are dose-dependent, efforts to reduce opioid consumption may mitigate these

harmful effects.[60,61] Therefore, reducing the reliance on opioids after CD is key to addressing acute opioid-related adverse events.

1.4 The opioid crisis

Since the 1990s, North America has been experiencing a crisis of opioid addiction and overdose.[62] In 2022 alone, there were 7,525 opioid-related deaths in Canada,[63] while in the United States, 81,806 people died from opioid overdoses.[64] Moreover, reports indicate that opioid consumption and opioid-related hospitalizations and deaths are increasing on virtually every continent.[65-69] The over-prescription of opioids by physicians has been identified as a contributing factor to the opioid crisis,[70] with many patients being first exposed to opioids as a part of their postoperative analgesia regimens after undergoing surgery.[71] In fact, an audit of opioid prescription in the United States reported that surgeons had the second highest rate of opioid prescribing across all medical specialities.[72] The risks associated with opioid prescription are two-fold. Firstly, patients who receive an opioid prescription after surgery may develop persistent opioid usage patterns, potentially leading to long-term dependency.[73] Secondly, opioid pills that are left unused after surgery may be diverted for non-medical use by family or community members.[74-76] For instance, in a Canadian study, children were 2.4 times more likely to die of an overdose if one of their parents had an opioid prescription.[77] Moreover, a survey of drug users found that more than half of people who recently misused pain medications reported acquiring them from family or friends.[78] Thus, reducing postoperative opioid over-prescription may mitigate opioid-related harms for patients and their surrounding communities, potentially playing a major role in addressing the opioid crisis.[65]

Excessive opioid prescribing at discharge after CD poses risks for patients and their communities. Recent studies reported that up to 86.7% of patients undergoing CD in the United

States receive an opioid prescription at discharge,[48] while more than 80% use only half or less of their prescription,[75] and 23.5-42% use no opioids post-discharge.[79,80] Rates of persistent postoperative opioid use after CD are generally lower compared to other surgical populations, with previous studies estimating a rate of 0.12-2.2% following CD,[81,82] compared to approximately 7% after general surgery.[73] Nonetheless, millions of patients undergo CD each year,[83] resulting in a substantial number of patients at risk for prolonged opioid use as well as a huge pool of unused opioids that are available for diversion and misuse. The ubiquity of CD makes this population an important target for reducing postoperative opioid prescription and consumption.

1.5 Research gap

Increased opioid consumption during postoperative stay is a risk factor for persistent use post-discharge.[84] However, previous research has demonstrated that opioid consumption and prescribing following CD is extremely variable,[85-87] indicating a need for a deeper understanding about current in-hospital opioid consumption and discharge prescribing patterns. Moreover, further evidence is required regarding modifiable patient and care factors associated with opioid consumption and prescribing following CD. Identifying and addressing these factors could potentially reduce opioid-related harms after CD and enhance postpartum outcomes.

1.6 Research aims

Given the research gap described above, the primary objectives of this thesis project were to (1) assess the extent to which opioids are prescribed and consumed during hospital stay after CD and (2) identify patient and care characteristics that are associated with opioid consumption at the postpartum ward. The secondary objectives of this thesis were to (1) compare in-hospital rates of

postoperative nausea and vomiting among opioid consumers verses non-consumers and (2) evaluate the rates and predictors of opioid prescribing at hospital discharge.

CHAPTER 2: MANUSCRIPT

Predictors of in-hospital opioid consumption and discharge prescribing following caesarean delivery.

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SHORT TITLE: Opioid analgesia after caesarean delivery

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TITLE

Predictors of in-hospital opioid consumption and discharge prescribing following caesarean delivery.

PRECIS

Following caesarean delivery, patient and care characteristics were associated with in-hospital opioid consumption, while pre-printed prescriptions were associated with the amount prescribed at discharge.

ABSTRACT

Objective: To estimate the extent to which patient and care characteristics are associated with in-hospital opioid consumption and discharge prescribing following caesarean delivery (CD).

Methods: This retrospective cohort study included patients undergoing CD under neuraxial anesthesia at a university-affiliated hospital from 12/2020-12/2021. Patient demographics, care characteristics, in-hospital opioid consumption, and discharge prescription (converted to morphine 5 mg pills) were collected from medical records. Data were analyzed using descriptive statistics and negative binomial regression.

Results: 904 patients were included (age 34.9±5 years, gestational age 38±3 weeks, multiple gestations 5.3%, previous CD 44.7%, emergency procedure 40.9%). In-hospital analgesia prescriptions included acetaminophen (100.0%), nonsteroidal anti-inflammatory drugs [NSAIDs] (91.2%), and opioids (100.0%). Only 45.5% of patients consumed opioids in-hospital (median consumption 0 [IQR 0-2] morphine 5 mg pills). Increased opioid consumption was associated with opioid use during pregnancy (Incidence Rate Ratio [IRR] 9.419 [95%CI 3.425-25.900]), higher postoperative pain (IRR 1.599 [95%CI 1.524-1.678)], and higher post-anesthesia care unit opioid consumption (IRR 1.007 [95%CI 1.002-1.013]). Decreased opioid consumption was associated with consuming NSAIDs (IRR 0.613 [95%CI 0.460-0.818]). Consuming opioids in-hospital was associated with increased length of stay (2.4±1.0 vs. 2.1±0.5 days, $p<0.001$), in-hospital postoperative nausea and vomiting [PONV] (28.1% vs. 19.6%, $p=0.003$), 30-day postoperative complications (13.2% vs. 7.1%, $p=0.002$), and hospital readmissions (2.4% vs. 0.6%, $p=0.025$). At discharge, 89.2% of patients were prescribed opioids (median 20 [IQR 20-20] morphine 5 mg pills). Reduced discharge opioid prescription was associated with receiving a pre-printed prescription with fewer pills (ten vs. twenty; IRR 0.548 [95%CI 0.389-0.770]).

Conclusion: In-hospital opioid consumption following CD was generally low and associated with certain patient and care factors. Consuming opioids was associated with increased length of stay, PONV, postoperative complications, and hospital readmissions. Discharge opioid prescription was only associated with preprinted prescription sizes. These findings can inform strategies to mitigate opioid-related harms following CD.

2.1 INTRODUCTION

Caesarean delivery (CD) is a common surgical procedure, accounting for over 20% of childbirths globally.[1] Effective pain management following CD is a top priority for patients and can greatly impact postpartum experiences and outcomes.[2] Adequate analgesia enhances postoperative recovery and facilitates the engagement in skin-to-skin contact and breastfeeding, which are fundamental for parent-infant bonding and overall well-being.[3]

Although opioids are widely prescribed for in-hospital analgesia after CD,[4] they often lead to adverse effects that hinder postoperative recovery, including drowsiness, dizziness, and postoperative nausea and vomiting (PONV).[5] Concerns also exist regarding opioid-related harms to breastfed infants, such as central nervous system and respiratory depression.[6] Notably, increased opioid consumption during postoperative stay is a risk factor for persistent use post-discharge, which may contribute to the ongoing opioid crisis.[7] Given the increasing rates of CD globally,[1] there is a critical need to minimize opioid harms after CD while ensuring effective postoperative pain management.

To enhance the quality of care after CD, it is essential to understand patients' current in-hospital analgesia requirements and identify modifiable factors associated with increased opioid consumption and prescribing. Therefore, the primary aims of this study were to (1) assess the extent to which opioids are prescribed and consumed during hospital stay after CD and (2) identify patient and care characteristics that are associated with opioid consumption. Secondarily, we (1) compared postoperative outcomes among in-hospital opioid consumers vs. non-consumers and (2) evaluated rates and predictors of opioid prescribing at hospital discharge.

2.2 METHODS

This retrospective cohort study was reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE)[8] guidelines (checklist available in Appendix, Table S1). Ethical approval was granted by our institutional research ethics board (MUHC REB ref: 2022-8532).

2.2.1 Participants and setting

We evaluated a consecutive sample of 904 patients who underwent CD a university-affiliated hospital in Montreal, Canada, from December 1, 2020 to December 31, 2021. This centre serves as a referral hub for high-risk obstetrical cases from across the province of Québec. To optimize the homogeneity of our study sample, we excluded patients (1) with poor preoperative physical status (American Society of Anesthesiologists [ASA] score > 3),[9] (2) who required general anesthesia, (3) who underwent a concomitant major surgical procedures (i.e., hysterectomies, cancer resection, or cardiac surgery), (4) who experienced trauma-induced delivery. All patients were treated within a care pathway including multimodal analgesia, early feeding, and early mobilization, with hospital discharge targeted for postoperative day (POD) 2. The choice of preoperative and intraoperative analgesia methods was at the discretion of the anesthesia team. Antiemetics were used as needed in the event of nausea or vomiting.

2.2.2 Data collection

Data concerning patient, procedure, and analgesia characteristics, as well as postpartum outcomes, were collected from electronic medical records (EMR) and entered into a REDCap database (https://www.project-redcap.org/).[10,11] The patient characteristics of interest included age, ASA score, comorbidities (classified according to the Obstetric Comorbidity Index tool[12]),

maternal history, gestational age, pregnancy complications, whether patients were in labor prior to caesarean. The procedure characteristics of interest included urgency (emergency or elective), type of skin and uterine incisions, surgery duration, additional procedures performed (i.e. sterilization, ovarian or paratubal cystectomy, myomectomy, lysis of adhesions, cerclage removal), and intraoperative complications.

Details regarding analgesia medications prescribed and consumed during hospital stay were collected, including those given in labor, intraoperatively, and postoperatively (i.e. type, dose, frequency, total amount, route of delivery). At hospital discharge, patients received a pre-printed discharge prescription, which clinicians could revise and edit at their discretion. The pre-printed form included fifty acetaminophen 1000 mg pills, twenty naproxen 500 mg pills, and twenty morphine 5 mg pills. Partway through the study period, a new pre-printed discharge prescription was introduced, which included the same amount of acetaminophen and naproxen, but only ten morphine 5 mg pills. We collected information about the analgesia medications prescribed at discharge including the type, dose, frequency, total amount, and if patients received the old or new pre-printed prescription.

The outcome in-hospital opioid consumption was defined as the amount of opioids consumed at the postpartum ward from POD0 to POD2, as most patients (79.7%) were discharged on POD2. The outcome opioid prescribing at discharge considered the amount of opioids included in patients' discharge prescriptions. We converted opioids of different strengths into morphine milligram equivalents (MMEs)[14] and, to facilitate the interpretation of our findings, standardized MMEs into an equivalent number of morphine 5mg pills, which is the drug and dosage most commonly prescribed at the study institution.

Postoperatively, we collected information relating to the highest pain score recorded at the postpartum ward (POD 0-2, measured using a 0-10cm Numerical Rating Scale), length of stay, Edinburgh Postnatal Depression Scale score, rates of in-hospital PONV (defined as any in-hospital nausea, retching, or vomiting requiring treatment with a rescue anti-emetic), in-hospital and 30-day postoperative complications, classified according to Clavien-Dindo[13] (definitions in the Appendix, Table S2), 30-day emergency room visits, and readmissions.

2.2.3 Sample size

Our sample size (n=904) provides sufficient power to accommodate up to 30 variables in the regression models focused on opioid consumption and prescribing (conservatively accounting for 30 subjects per variable).[15] Moreover, this sample size provides sufficient power to accommodate up to 9 variables in our *post hoc* regression focused on opioid-free discharge prescription (considering an event rate of ~10% and 10 subjects per event).[16]

2.2.4 Data Analysis

All statistical analyses were performed using Stata® version 17 software (StataCorp, College Station, TX, USA).[17] Continuous variables were summarized using means, standard deviations (SDs), medians, interquartile ranges (IQR), and number of observations, as appropriate. Categorical variables were summarized using frequencies and percentages. In-hospital opioid consumption and discharge prescription (in number of morphine 5 mg pills) were analyzed using descriptive statistics. Predictors of these outcomes were analyzed using multivariate negative binomial regressions to produce Incidence Rate Ratios (IRRs). The selection of potential predictors included in the regression models was based on findings from previous literature and clinical plausibility (Table 1). The justification for the inclusion of each potential predictor is available in the Appendix (Table S3). Stepwise backward selection was performed for variable

reduction, retaining those with p-value < 0.10.[18] There was no missing data for in-hospital outcomes (i.e., in-hospital opioid consumption). The analysis of discharge opioids excluded patients with prescriptions missing from EMRs (n=28, [3.1%]). Missing data for predictor variables were addressed using multiple imputations by chained equations with predictive mean matching, combining 50 simulations using Rubin's rules.[19] Adjusted and unadjusted analyses of predictors are reported. To further assess the robustness of our primary regression models, we conducted post hoc sensitivity analyses, including: (1) full models without stepwise elimination of variables, (2) without multiple imputation, (3) excluding outliers (patients who consumed more than 50 MME per day[20], n=49 [5.4%]), and (4) calculating ward opioid consumption across the entire stay at the postpartum ward (POD0 to discharge). To explore the association of in-hospital opioid consumption vs. no consumption with postoperative outcomes (in-hospital PONV, length of stay, 30-day complications, emergency room visits, and readmissions) we used Chi-Squared, Fisher Exact, or Mann Whitney U tests, as appropriate. Statistical significance was based on 95% confidence intervals excluding the null, or p-value < 0.05.

2.3 RESULTS

A total of 973 patients underwent CD during the study period, 69 met exclusion criteria, and 904 were included in our primary analysis (study flow diagram and reasons for exclusion in Figure 1). Patient and surgical characteristics are reported in Table 2. The included patients had a mean age of 34.9 years (± 5.1 years) and a mean gestational age of 38.1 weeks (± 2.8 weeks). A total of 404 patients (44.7%) had undergone a previous caesarean delivery. Only 4 patients (0.44%) used opioids during pregnancy. 376 patients (41.6%) were diagnosed with at least one pregnancy-related complication (Table 2). There were 370 emergency CD (40.9%), while 534 (57.1%) were elective. Approximately half of patients experienced labor before their caesarean

delivery (n=432, [47.8%]). The most common indication for caesarean were repeat elective caesareans (n=350, [38.7%]). The most common concomitant procedure was sterilization (n=96 [10.6%]). The mean procedure duration was 46.9 minutes (±15.8 minutes).

In-hospital analgesia

Preoperative, intraoperative, and postoperative analgesia regimens are reported in Table 3. Most of the patients who received preoperative analgesia (n=228, [25.2%]) were administered combined fentanyl and bupivacaine via epidural (as labour analgesia). Intraoperatively, all patients received neuraxial anesthesia (spinal n=647 [71.6%], epidural n=251 [21.8%], combined spinal-epidural n=6 [0.66%]. Typically, spinal anesthesia consisted of morphine and bupivacaine; epidural anesthesia consisted of lidocaine and morphine, with some patients receiving additional fentanyl. None of the patients continued receiving neuraxial analgesia after discharge from the operating room, and no patients received peripheral nerve blocks or local anesthesia infiltrations.

In the post-anesthesia care unit (PACU), most patients (n=899, [99.45%]) consumed non-opioid analgesics (acetaminophen n=898 [99.3%], non-steroidal anti-inflammatory drugs [NSAIDs] n= 64 [7.0%]). Approximately half of the patients, consumed opioids in the PACU (n=420 [46.5%]), most commonly morphine (n=396 [43.8%]; intravenous n=218 [24.12%], oral n=188 [20.8%], subcutaneous n=40 [4.4%]), with a minority of patients receiving other opioid drugs (hydromorphone n=6 [0.66%], fentanyl n=3 [0.33%]).

The median highest postoperative pain score at the postpartum ward from POD0-2 was 5 (IQR 3-7). All patients (n=904, [100%]) were prescribed both non-opioid and opioid analgesics at the ward (acetaminophen n=904 [100%]; NSAIDs n=824 [91.2%]; opioids n=904 [100%]). All patients consumed analgesics orally (n=904 [100%]), with a minority receiving intravenous (n=108 [12%]), rectal (n=39 [4.3%]), or subcutaneous analgesics (n=24 [2.7%]). Most patients

consumed acetaminophen (n=898 [99.3%] and NSAIDs (n=804 [88.94%]; naproxen n=803 [88.8%]%). Opioids were consumed by 410 patients (45.4%), most commonly morphine (n=351 [38.8%]). Up to POD2, the median MMEs consumed at the ward was 0 (IQR 0-10) (mean 9.65±40.53 MME), which is equivalent to 0 (IQR 0-2) morphine 5 mg pills (mean 1.87±8.07 pills). Among patients who consumed opioids, the median consumption was 12.5 MME (IQR 5-22.5) (mean 21.3±58.1 MME), the equivalent to 2 (IQR 1-4) morphine 5 mg pills (mean 4.1±11.6 pills).

Among the 876 patients (96.9%) with discharge prescriptions available in their EMRs, 874 (99.8%) were prescribed acetaminophen, 813 (92.8%) were prescribed NSAIDs (naproxen n=813 [92.8%]), and 781 (89.2%) were prescribed an opioid (morphine n=767 [87.6%], hydromorphone n=16 [1.8%], oxycodone n=2 [0.2%]). A total of 838 patients (95.7%) received a pre-printed prescription with twenty morphine 5 mg pills and 38 patients (4.3%) received a prescription with ten morphine 5 mg pills. The median amount of opioids prescribed at discharge was 100 MME (IQR 100-100; mean 87.64 ± 41.28 MME), or twenty 5 mg morphine pills (IQR 20-20; mean 17.53 ± 8.26 pills). A total of 95 patients (10.9%) received opioid-free discharge analgesia prescriptions.

Predictors of in-hospital opioid consumption and discharge prescription

The patient and care-related characteristics significantly associated with increased opioid consumption at the postpartum ward included opioid use during pregnancy (vs. none) (IRR 9.419 [95%CI 3.425 to 25.900]), higher pain scores on POD0-2 (IRR 1.599 [95%CI 1.524 to 1.678)], and higher PACU opioid consumption (IRR 1.007 [95%CI 1.002 to 1.013]), while decreased opioid consumption was associated with consuming NSAIDs (IRR 0.613 [95%CI 0.460 to 0.818]) (Table 4) (univariate analysis in Appendix, Table S4; complete model before stepwise

regression in Appendix, Table S5). Sensitivity analyses without imputations, excluding outliers, and calculating opioid consumption across the entire length of stay supported the results of the primary analysis (Appendix, Tables S6-S11).

Among the potential predictors of opioid discharge prescription included in our regression analysis, only receiving a preprinted prescription form with 10 morphine pills (vs. 20 pills) was a significant predictor of decreased opioid prescription at discharge (IRR 0.548 [95%CI 0.389 to 0.770]) (Table 4) (univariate analysis in Appendix, Table S12; complete model before stepwise regression in Appendix, Table S13). In-hospital opioid consumption was not a significant predictor of discharge prescription. Sensitivity analysis without stepwise selection and without multiple imputations supported these findings (Appendix, Tables S14-S17).

Other postoperative outcomes

The median length of stay was 2 days (IQR 2-2) (Table 2). A total of 212 (23.5%) patients experienced in-hospital PONV. 30-day postoperative complications (other than PONV) were experienced by 90 patients; 32 patients (3.5%) during primary hospital stay, 62 (6.9%) post-discharge (Table 2). Most complications were minor to moderate (Clavien-Dindo Grade 1: 2.3%, Grade 2: 7.9%). A full list of complication rates, definitions, and Clavien-Dindo grades are in the Appendix (Table S2). Healthcare reutilization within 30 days of discharge included 11 patients (1.2%) visiting the emergency department and 13 patients (1.4%) readmitted to hospital.

In-hospital opioid consumption (vs. no consumption) was significantly associated with longer length of stay (2.4±1.0 days vs. 2.1±0.5 days, $p<0.001$) and higher incidence of in-hospital PONV (28.1% vs. 19.6%, $p=0.003$), 30-day postoperative complications (13.2% vs. 7.1%, $p=0.002$), and hospital readmissions (2.4% vs. 0.6%, $p=0.025$) (Appendix, Table S18). In-

hospital opioid consumption was not associated with emergency department visits (1.2% vs. 1.2%, p=0.613).

2.4 DISCUSSION

The results of this cohort study support that in-hospital opioid consumption following CD is generally low. Predictors of increased opioid consumption included opioid use during pregnancy, higher pain scores, higher opioid consumption during PACU stay, and not using NSAIDs. In-hospital opioid consumption was associated with longer hospital stays and higher incidences of in-hospital PONV, 30-day postoperative complications, and hospital readmissions. At hospital discharge, the number of pills indicated on the preprinted discharge prescription was the only factor associated with the amount of opioids prescribed. Our study's strengths include its large sample size, robust statistical analysis plan, and compliance with STROBE reporting guidelines. Given its robust design, we believe that this study contributes relevant data to inform strategies mitigating opioid-related harms following CD.

Our results corroborate previous research indicating that opioid consumption during pregnancy is associated with increased postoperative opioid consumption,[21] which may be associated with additional sources of pain or opioid-induced hyperalgesia.[22] However, this finding is based on very few patients who consumed opioids preoperatively (n=4) and may represent exceptional cases. This and other predictors, such as pain intensity and opioid use in the PACU, underscore specific patient profiles that may benefit from optimized multimodal analgesia to reduce postoperative opioid requirements. Our centre's standard analgesia regimen complies with guidelines recommending the prescription NSAIDs to manage pain after CS.[23] However, some patients (n=83) did not use NSAIDs and tended to consume more opioids. While many of these patients may not have taken NSAIDs due to contraindications (i.e., allergy, kidney disease), this

result supports that, when not contraindicated, multimodal analgesia with NSAIDs is a valuable strategy to reduce postpartum opioid consumption.

Our findings suggest that opioid-free analgesia is feasible for many patients, as only 45% consumed opioids during their postpartum ward stay. We cannot exclude that opioid-free rates could have been higher with the use of wound anesthetic infiltration or nerve blocks, particularly when intrathecal morphine was not utilized.[23,24] Furthermore, despite recommendations by guidelines,[23,24] non-pharmacological interventions such as cryotherapy (i.e., icepacks), electrotherapy (i.e., transcutaneous electrical nerve stimulation), and relaxation (i.e., meditation) have been understudied in CD patients, with studies generally having small sample sizes and low methodological quality.[25] However, research involving other surgical populations has promising results; for example, a recent meta-analysis supports that postoperative cryotherapy may reduce patient-reported pain intensity and opioid consumption.[26] The potential benefits of non-pharmacological pain interventions after CD warrants further research. Our results suggest that promoting in-hospital opioid-free analgesia may reduce opioid-related harms such as PONV. We also found that in-hospital opioid consumption was associated with prolonged length of stay, 30-day complications, and readmissions, but the potential causality of this relationship should be assessed in future studies.

In our study, the number of opioid pills prescribed at discharge was not influenced by patient or care characteristics and was only associated with the preprinted discharge prescription. This corroborates previous research showing that changing preprinted prescriptions is a simple and effective way to reduce post-discharge opioid use.[27] While preprinted prescriptions offer convenience and standardization, they limit flexibility in tailoring analgesia to individual patient needs. Although clinicians in our study could amend preprinted prescriptions as needed, in-

hospital opioid consumption was not associated with discharge prescribing, suggesting that this factor was often overlooked in the discharge prescribing decision-making process. Previous research supports that tailoring opioid discharge prescribing based on in-hospital consumption, such as providing opioid-free discharge for patients who consumed no opioids in-hospital, significantly reduced opioid consumption without negatively impacting pain scores or satisfaction.[27]

Our study has several limitations. As our setting was a referral centre for high-risk pregnancies, our results may not be generalizable to general obstetric practice settings or to patient groups not included in our analyses (e.g., those undergoing general anesthesia). Our definition of PONV, requiring treatment with an anti-emetic, may underestimate the incidence of this outcome in comparison to studies using broader definitions. As our study primarily relied on EMR data, we did not conduct follow-up evaluations of opioid consumption post-discharge. A recent meta-analysis supports that opioid prescribing at surgical discharge does not reduce pain intensity but does increase adverse events.[28] Notably, only one trial investigated opioid-free pain management following CD,[29] highlighting the need for further comparative-effectiveness studies in this field.

Given increasing rates of CD globally,[1] these patients are an important target for quality improvement initiatives aiming to reduce opioid over-prescription. Our findings suggest that opioid-free analgesia is feasible for many patients in the postpartum ward, potentially signalling decreased post-discharge opioid requirements.

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TABLES

Table 1: Potential predictors of in-hospital opioid consumption and discharge prescription

Predictors of in-hospital opioid consumption
Age (years)
ASA Score [*]
Previous caesarean
Multiple gestation
Pregnancy complications
Smoking during pregnancy
Opioid use during pregnancy
Mental health disorder [†]
Edinburgh Postnatal Depression Score
Urgency level [‡]
Labor before caesarean
Concomitant procedure [§]
Surgery duration
Intra-operative complications or postoperative complications during primary stay
Received NSAIDs in-hospital
Highest postoperative pain score at the postpartum ward POD0-2 [‖]
PACU opioid consumption [¶]
Additional predictors of opioid prescribing at discharge
Length of stay
In-hospital opioid consumption [#]
Discharge prescription included NSAIDs
Preprinted prescription form with 10 vs. 20 morphine pills

ASA: American Society of Anesthesiologists, NSAIDs: non-steroidal anti-inflammatory drugs, POD: postoperative day, PACU: post-anesthesia care unit. [*]Dichotomized as ASA = 3 vs. ASA < 3. [†]Includes anxiety, depression, bipolar disorder. [‡]Emergency vs. Elective. [§]Includes tubal ligation and salpingectomy, ovarian and para-tubal cystectomy, myomectomy, cerclage removal, lysis of abdominal adhesions, repair of previous dehiscence, vaginal laceration repair, lipoma removal. [‖]Highest score from postoperative days 0-2, measured using a 0-10 Numerical Rating Scale. [¶]Measured in milligram morphine equivalents (MME). [#]Measured in equivalent number of morphine 5 mg pills.

Table 2: Patient demographics, surgery characteristics, and postoperative outcomes

Patient characteristics	N = 904
Age (years)	34.92 ± 5.14
ASA score *	
1	130 (14.59%)
2	646 (72.50%)
3	115 (12.91%)
Gestational age (weeks)	38.13 ± 2.84
Gravidity	2 [1-4]
Parity	1 [0-1]
Multiple gestation	48 (5.31%)
Previous caesarean section	404 (44.69%)
Pregnancy complications	376 (41.59%)
Gestational diabetes	193 (21.35%)
Preeclampsia	75 (8.30%)
Chorioamnionitis	41 (4.54%)
PPROM	33 (3.65%)
Gestational hypertension	31 (3.43%)
Placenta previa	26 (2.88%)
Maternal fever	21 (2.32%)
HELLP	8 (0.88%)
Placental abruption	6 (0.66%)
Uterine rupture	2 (0.22%)
Mental health disorder	89 (9.85%)
Anxiety	62 (6.86%)
Depression	48 (5.31%)
Bipolar disorder	4 (0.44%)
Smoking during pregnancy †	33 (4.12%)
Taking opioids during pregnancy	4 (0.44%)
EPDS score ‡	4 [1-7]
Obstetric Comorbidity Index [12]	2 [1-3]
Labor before caesarean	432 (47.79%)
Indication for caesarean	
Repeat elective	350 (38.72%)
Fetal condition	164 (18.14%)
Prolonged or arrested labor	135 (14.93%)
Fetal presentation	112 (12.39%)
Pregnancy complication	63 (6.97%)
Maternal health condition	38 (4.20%)
Multiple gestation	24 (2.65%)
Maternal choice	18 (1.99%)
Surgical characteristics	

Urgency	
Elective	534 (59.07%)
Emergency	370 (40.93%)
Skin incision	
Pfannenstiel	904 (100%)
Uterine incision [§]	
Low transverse	889 (98.78%)
Classical	5 (0.56%)
T extension	5 (0.56%)
Other	1 (0.11%)
Concomitant procedures	120 (13.27%)
Sterilization	96 (10.62%)
Cyst removal	11 (1.22%)
Cerclage removal	8 (0.89%)
Lysis of adhesions	6 (0.66%)
Myomectomy	4 (0.44%)
Lipoma removal	1 (0.11%)
Intraoperative complications	31 (3.44%)
Injury to other viscera	16 (1.77%)
Hemorrhage	14 (1.55%)
Vascular injury	6 (0.66%)
Other	6 (0.66%)
Surgery duration (minutes)	46.89 ± 15.75
Postoperative outcomes	
Highest postoperative pain score (postpartum ward POD0-2)	5 [3-7]
Length of stay (days)	2 [2-2] 2.3 ± 1.1
In-hospital PONV	212 (23.5%)
30-Day Postoperative Complications (excluding PONV)	90 (9.96%)
During primary stay	32 (3.54%)
Post-discharge	62 (6.75%)
Clavien-Dindo Classification [13]	
1	232 (25.66%)
2	72 (7.95%)
3b	2 (0.22%)
4a	1 (0.11%)
30-day Emergency Department Visit	11 (1.22%)
30-day Readmission	13 (1.44%)

Data are reported as frequency n(%), mean ± SD, or median [IQR]. ASA: American Society of Anesthesiologists, PPROM: Preterm Premature Rupture of Membranes, HELLP: Hemolysis Elevated

Liver enzymes and Low Platelets, EPDS: Edinburgh Postnatal Depression Scale, SD: standard deviation, IQR: inter-quartile range, POD: postoperative day, PONV: postoperative nausea and vomiting. [*] *Missing data n = 13 (1.44%).* [†] *Missing data n = 103 (11.39%).* [‡] *Missing data n = 72 (7.97%).* [§] *Missing data n = 4 (0.42%).*

Table 3: Analgesia regimen characteristics

Pre-operative Analgesia	N = 904
Non-opioids	161 (17.81%)
Acetaminophen PO	139 (15.38%)
Lidocaine (epidural)	46 (5.09%)
Ketorolac IV	5 (0.55%)
Opioids	263 (29.09%)
Fentanyl-Bupivacaine (epidural)	228 (25.22%)
Morphine SC PO	76 (8.41%) 48 (5.31%) 28 (3.10%)
Fentanyl IV	12 (1.33%)
Hydromorphone IV or SC	2 (0.22%)
Nalbuphine IV *	1 (0.11%)
Total pre-operative opioid consumption in MME	0 [0-17.2] 70.55 ± 159.93
Intraoperative Anesthesia	N = 904
Spinal (morphine, bupivacaine)	647 (71.57%)
Epidural (morphine, lidocaine, ± fentanyl)	251 (27.77%)
Combined Spinal-Epidural (morphine, bupivacaine, ± lidocaine, ± fentanyl)	6 (0.66%)
PACU Analgesia	N = 904
Non-Opioids	899 (99.45%)
Acetaminophen PR or PO	898 (99.3%)
Naproxen PO	63 (6.97%)
Ketorolac IV	1 (0.11%)
Opioids	420 (46.46%)
Morphine IV PO SC	396 (43.81%) 218 (24.12%) 188 (20.80%) 40 (4.42%)
Meperidine IV †	21 (2.32%)
Nalbuphine IV *	18 (1.99%)
Hydromorphone IV SC	6 (0.66%) 3 (0.33%) 3 (0.33%)
Fentanyl IV	3 (0.33%)
Oxycodone PO	1 (0.11%)
Total PACU opioid consumption in MME	0 [0-12.5] 9.52 ± 16.40

Postpartum Ward Analgesia Prescription	N = 904
Non-Opioids	904 (100.00%)
Acetaminophen PO	904 (100.00%)
Naproxen PO	824 (91.15%)
Opioids	904 (100.00%)
Postpartum Ward Analgesia Consumption	N = 904
Non-Opioids	904 (100.00%)
Acetaminophen PO	898 (99.34%)
Naproxen PO	803 (88.83%)
Ketorolac IV	2 (0.22%)
Opioids	410 (45.44%)
Morphine PO SC IV	351 (38.83%) 338 (37.39%) 19 (2.10%) 2 (0.22%)
Hydromorphone PO SC IV	31 (3.43%) 24 (2.65%) 7 (0.77%) 3 (0.33%)
Oxycodone PO	3 (0.33%)
Fentanyl IV	1 (0.11%)
Nalbuphine IV *	102 (11.28%)
Patients consuming NSAIDs in hospital	821 (90.8%)
In-hospital opioid consumption POD0-2 in MME	0 [0-10] 9.65 ± 40.53
In-hospital opioid consumption POD0-2 in morphine 5 mg pills	0 [0-2] 1.87 ± 8.07
Post-discharge Analgesia Prescription	N = 876
Non-Opioids	876 (100.00%)
Acetaminophen (1000mg, every 4-6 hrs, PRN)	874 (99.77%)
Naproxen (500 mg, PO, every 12 hrs, PRN)	813 (92.81%)
Opioids	781 (89.16%)
Morphine (5-10 mg, PO, every 4-6 hrs, PRN)	767 (87.56%)
Hydromorphone (1-3 mg, PO, every 4-6 hrs, PRN)	16 (1.83%)
Oxycodone (5-10 mg, PO, every 4-6 hrs, PRN)	2 (0.23%)
Pre-printed discharge prescription form Twenty morphine 5 mg pills Ten morphine 5mg pills	 838 (95.66%) 38 (4.34%)
Opioids prescribed at discharge in MME	100 [100-100]

	87.64 ± 41.28
Opioids prescribed at discharge in 5 mg morphine pills	20 [20-20] 17.53 ± 8.26

Data are reported as frequency n(%), mean ± SD, or median [IQR]. PO: "per os" oral medication, IV: intravenous, SC: subcutaneous, PR: per rectum, PACU: Post Anesthesia Care Unit, MME: Milligram Morphine Equivalents, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: post-operative day, PRN: "pro re nata" as needed, IQR: inter-quartile range, SD: standard deviation. [*] *Administered for itching.* [†] *Administered for shaking.*

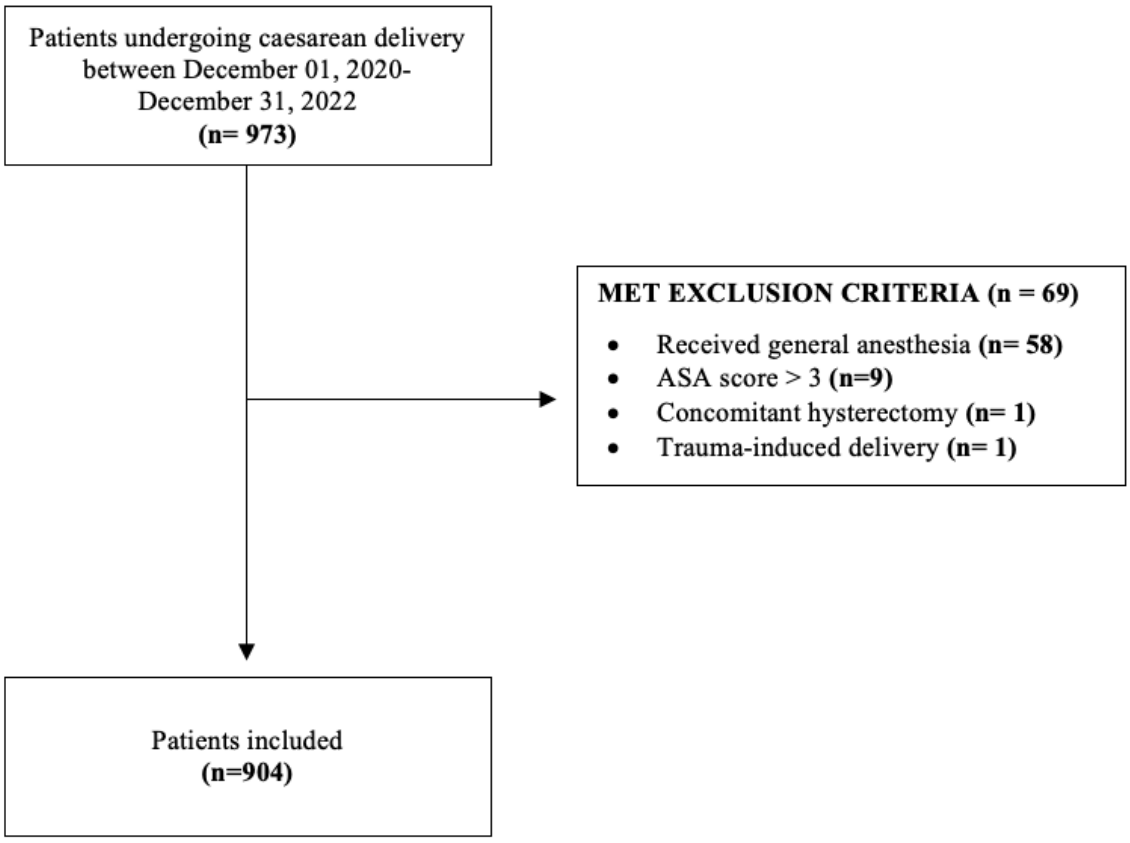
Table 4: Predictors of in-hospital opioid consumption and opioid prescription at discharge (in number of morphine 5 mg pills).

Predictor	**IRR [95% CI]**	**p-value**
In-hospital opioid consumption (N=904)		
Opioid use during pregnancy (vs. none)	9.419 [3.425 to 25.900]	**< 0.001**
Emergency (vs. elective)	1.203 [0.986 to 1.469]	0.069
Received NSAIDs in hospital (vs. none)	0.613 [0.460 to 0.818]	**0.001**
Highest pain score POD0-2	1.599 [1.524 to 1.678]	**< 0.001**
PACU opioid consumption in MME (higher)	1.007 [1.002 to 1.013]	**0.006**
Opioids prescribed at discharge (N=876)		
Preprinted prescription form with 10 morphine pills (vs. 20 pills)	0.548 [0.389 to 0.770]	**0.001**

Negative binomial regression analysis with backwards stepwise selection and multiple imputations for missing predictor data. IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anaesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day, PACU: post-anesthesia care unit, MME: milligram morphine equivalents.

FIGURES

Figure 1: Patient inclusion flow diagram



ASA: American Society of Anesthesiologists.

CHAPTER 3: CONCLUSIONS AND FUTURE DIRECTIONS

Increased in-hospital postoperative opioid consumption is associated with numerous risks for CD patients, including adverse events that hinder postoperative recovery[52] and may negatively affect parent-infant bonding and overall outcomes.[54-56] Furthermore, the over-prescription of opioids at discharge following CD may facilitate opioid misuse by patients other community members, contributing to the current opioid crisis.[74-76] This thesis research sheds light on important aspects of in-hospital opioid consumption and discharge prescription following CD and their potential impact on postpartum outcomes. Our findings highlight a need for more judicious opioid prescribing practices and further investigation of alternative pain management strategies after CD.

Our study supports that a large proportion of patients does not consume opioids at the postpartum ward and may be suitable candidates for opioid-free postoperative analgesia. Implementing opioid-free in-hospital analgesia may further decrease the number of patients exposed to opioids and reduce rates of opioid-related adverse events. Moreover, previous research supports that in-hospital opioid consumption is a predictor of chronic opioid use post-discharge.[84] Opioid-free analgesia during hospitalization and after discharge may effectively reduce the number of unused pills introduced into communities.[88-90]

Outside of North America, opioid-free postoperative analgesia is a common practice and has been shown to yield similar or superior pain-related outcomes in comparison with opioid analgesia.[91-94] For instance, a cohort study found that surgical patients in Europe reported better postoperative pain scores, reduced pain interference, and decreased opioid consumption in comparison with patients in the United States.[95] Although several trials have compared in-hospital opioid versus opioid-free analgesia following CD,[96-98] their results are varied with

respect to outcomes and there appear to be no knowledge syntheses summarizing their results.[99] A recent meta-analysis also supported that opioid-free analgesia after surgical discharge does not increase postoperative pain scores and is associated with fewer adverse events in comparison with opioid analgesia;[88] however, only one of the identified trials involved patients undergoing CD.[100] Robust comparative-effectiveness research is essential for establishing evidence-based guidelines that can inform postoperative opioid prescribing following CD.

Such research may also help further explore the potential causality relationships between opioid-free analgesia and improved post-discharge outcomes, as observed in our study. Although in-hospital opioid use was associated with prolonged length of stay, 30-day complications, and readmissions, our study was retrospective and we had limited access to post-discharge data. This restricts our ability to interpret if the observed associations are causal (i.e., opioid use directly impact outcomes) or merely correlational (i.e., opioid use is a marker of other factors that impact outcomes [e.g., comorbidities, birth complications]). The findings of this thesis highlights the need for further research in this field.

Our study corroborates previous research showing that the number of pills prescribed at discharge is not associated with clinical factors or inpatient opioid consumption, highlighting a need to investigate prescribing decision-making among obstetricians.[87,101] Several approaches for individualizing discharge prescriptions exist in the literature, including creating opioid prescribing nomograms based on patient characteristics,[49] tailoring discharge prescriptions based on in-hospital opioid consumption,[90,102,103] and allowing patients to opt out from receiving opioids postoperatively.[104] Studies focused on these approaches report a considerable reduction in opioid prescription, consumption, and unused pills without a change in postoperative pain scores or readmissions.[90,102-104] While the PROSPECT Working Group recommends stratifying

post-discharge analgesia prescriptions based on patients' needs,[25] several studies have highlighted a lack of universally accepted standards regarding the appropriate amount of opioids to be prescribed at discharge following CD.[105-107] Given that opioid prescription size is associated with persistent opioid use after surgical discharge[84] and that discharge prescriptions can be a relevant source of opioid diversion,[48,75,79,80] there is an urgent need for further research aiming to optimize discharge analgesia prescribing decision-making after CD.

Future research investigating peripartum analgesia should address existing inequities in pain management. The undertreatment of pain and postoperative complications in People of Colour is a systemic issue, particularly in obstetrics and gynaecology.[108,109] There is a breadth of literature describing racial disparities in peripartum pain management; for example, cohort studies by Glance et al. and Badreldin et al. support that Black and Hispanic patients are less likely to receive epidural anesthesia in labour and opioid prescriptions at discharge, despite reporting higher pain scores than White patients.[110,111] Indigenous patients are also at higher risk of experiencing discrimination and adverse postoperative and peripartum outcomes. Previous studies support that Indigenous patients experience higher rates of postoperative mortality and complications across surgical specialties,[112] as well as higher incidences of pregnancy complications and adverse birth outcomes compared to non-Indigenous patients.[113,114] Furthermore, Indigenous patients are at risk of experiencing discrimination from healthcare professionals, which may impact how analgesics are prescribed. In qualitative studies interviewing healthcare professionals and Indigenous patients, stereotypes and discriminatory attitudes about drug use were identified as barriers for Indigenous patients seeking care.[115-118] While there is ample evidence supporting that racism and other socio-cultural factors can influence analgesic prescription and consumption after CD,[119-121] research relying on

retrospective data from medical records, such as our study, may overlook the impact of discrimination and inequitable care on pain outcomes. Possible ways to address these disparities include education for health care professionals,[122,123] as well as standardized pain management protocols[124] and ERAS pathways,[125] which have previously reduced racial and gender disparities in perioperative care and analgesia. In future studies, researchers are encouraged to engage with community stakeholders and organizations to better understand, investigate, and address inequities in pain management following CD.[126]

In summary, this thesis research supports that in-hospital opioid consumption following CD is generally low, with certain patient and care factors associated with increased opioid use. The consumption of opioids was associated with longer length of stay, increased risk of nausea and vomiting, postoperative complications, and hospital readmissions. At discharge, the use of preprinted prescriptions was the sole factor associated with the quantity of opioids prescribed. These findings offer valuable insights that can guide strategies and future research endeavors aimed at mitigating opioid-related harms following CD.

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APPENDIX

Table S1. STROBE Statement Checklist

Item No		Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	24-26
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	25-26
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	27
Objectives	3	State specific objectives, including any prespecified hypotheses	27
Methods			
Study design	4	Present key elements of study design early in the paper	27-31
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	28-29
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	28-29, Figure 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	28-32, Table 1, Appendix Table S2-3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	28-30
Bias	9	Describe any efforts to address potential sources of bias	28-31
Study size	10	Explain how the study size was arrived at	30
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	28-31, Table 1, Appendix Table S3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	30-31, Appendix Tables S4-17
		(*b*) Describe any methods used to examine subgroups and interactions	Appendix Tables S4-17
		(*c*) Explain how missing data were addressed	30
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	30-31, Appendix Tables S4-17
Results			
Participants1	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	31-35, Figure 1
		(b) Give reasons for non-participation at each stage	31, Figure 1
		(c) Consider use of a flow diagram	

Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	31-35, Tables 2-3
		(b) Indicate number of participants with missing data for each variable of interest	Tables 2-3
		(c) Summarise follow-up time (e.g., average, and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	31-35, Tables 2-4, Appendix Table S18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	33-34, Table 4, Appendix Tables S4, S12, S18
		(*b*) Report category boundaries when continuous variables were categorized	Tables 1-4, Appendix Table S18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	33-34, Appendix Tables S4-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	34-35
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	35-37
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	35-37
Generalisability	21	Discuss the generalisability (external validity) of the study results	35-37
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Not applicable

**Give information separately for exposed and unexposed groups.*

Note: *An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.*

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Table S2: Rates and Definitions of Postoperative 30-day Complications (N=904)

Complication	Frequency n (%)
Clavien Dindo[1] Grade 1	
Wound dehiscence: Separation of the incision of 1 cm or longer requiring closure with Steri-strips or operative closure. [2,3]	10 (1.1%)
Urinary retention: Reinsertion of indwelling urinary catheter after removal attempt or patient discharged with urinary drainage (excluding patients with permanent indwelling urinary catheter).[4]	5 (0.6%)
Superficial vein thrombosis: SVT appears as a red, hot, palpable tender cord in the course of a superficial vein.[5,6]	2 (0.2%)
Post-dural puncture headache: Persistent postural headache related to puncture of the dura mater during epidural catheter placement.[7]	2 (0.2%)
Generalized edema: Presence of pitting on the limbs and/or trunk, treated with diuretics.[8]	2 (0.2%)
Clavien Dindo Grade 2	
Surgical site infection: Visible pus and/or cellulitis without pus, with or without positive culture, or any sign or symptom of infection (e.g. pain, tenderness, localized swelling and/or redness) at the superficial incision requiring antibiotics.[9,10]	37 (4.1%)
Urinary tract infection: Upper or lower urinary symptoms and presence and growth of microbial pathogens in the urinary tract requiring antibiotics [11,12]	16 (1.8%)
Postoperative bleeding: Any postoperative bleeding (e.g. intra-abdominal, gastrointestinal) requiring blood transfusion or intravenous iron after surgery, or the need for reintervention.[1,13]	13 (1.4%)
Endometritis: Inflammation and infection of the decidua, characterized by fever, fundal tenderness, and purulent discharge from the uterus, requiring antibiotics.[14]	2 (0.2%)
Postoperative ileus: Abdominal distention or intolerance of solid food intake or inability to pass gas or stool beyond POD3, unrelated to any other ongoing complication and requiring placement of an NG tube.[15,16]	1 (0.1%)
Deep vein thrombosis: Radiological confirmation of DVT or anticoagulation started due to clinical findings.[17]	1 (0.1%)
Pulmonary embolism: Radiological evidence of pulmonary embolism or anticoagulation started due to clinical findings.[18,19]	1 (0.1%)
Clavien Dindo Grade 3a	
Acute Pancreatitis: Diagnosis requires 2 of the following: upper abdominal pain of acute onset often radiating through to the back; increase in serum amylase or lipase (x3 normal value); cross-sectional abdominal imaging consistent with acute pancreatitis.[20]	1 (0.1%)
Clavien Dindo Grade 3b	
Retained products of conception: Presence of trophoblastic tissue in the uterus, requiring reoperation, operative hysteroscopy, or dilation and curettage.[21]	1 (0.1%)
Clavien Dindo Grade 4a	
Heart failure: Clinical or radiological signs of congestive heart failure and specific treatment initiated.[22,23]	1 (0.1%)

SVT: superficial vein thrombosis, POD: postoperative day, NG: nasogastric, DVT: deep vein thrombosis

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Table S3: Justification of potential predictor variables for regression analyses

Predictors of in-hospital opioid consumption	
Age (years)	Older age was associated with decreased postoperative opioid consumption.[1]
ASA Score,	Higher ASA score was associated with increased postoperative opioid consumption in caesarean delivery patients,[2] and in other surgical populations.[1]
Previous caesarean,	Patients undergoing repeat caesarean delivery had lower postoperative pain scores and opioid consumption than patients undergoing primary caesarean delivery.[3]
Multiple gestation	Multiple fetuses are associated with additional demands on pregnant patients' bodies and increased risk of pregnancy complications, which may impact postoperative pain following caesarean delivery.[4]
Pregnancy complications	Gestational diabetes was associated with higher postoperative opioid consumption following caesarean delivery.[5]
Smoking during pregnancy	Smoking was associated with increased post-discharge opioid consumption following caesarean delivery.[1,6]
Opioid use during pregnancy	Caesarean delivery patients taking buprenorphine for opioid use disorder during pregnancy consumed more opioids postoperatively than matched controls who did not consume buprenorphine.[7]
Mental health disorder	Caesarean delivery patients with depression or anxiety had higher postoperative pain scores and opioid consumption.[6,8]
Edinburgh Postnatal Depression Score	Higher antepartum EPDS scores were associated with increased postoperative opioid consumption.[9,10]
Urgency level	Emergency caesarean was associated with increased opioid consumption.[11] Emergency caesarean delivery may also have psychological impacts on postoperative pain.[12]
Labor before caesarean	Labor before caesarean delivery was associated with increased post-discharge opioid consumption.[13]
Concomitant procedure	Caesarean delivery with bilateral tubal was associated with higher opioid consumption in-hospital in comparison with caesarean delivery alone.[14]
Surgery duration	Longer surgery duration was associated with higher postoperative pain following caesarean delivery.[15]
Intra-operative complications or postoperative complications during primary stay	Postoperative complications were associated with increased and prolonged postoperative pain.[16]
Received NSAIDs in-hospital	ERAS guidelines recommend multimodal postoperative analgesia including acetaminophen and NSAIDs following caesarean delivery.[17]
Highest postoperative pain score at the postpartum ward POD0-2	Higher pain scores at postoperative discharge were associated with increase post-discharge opioid consumption.[18]
PACU opioid consumption	Increased PACU opioid consumption was associated with increased opioid consumption in the first 24h after caesarean delivery.[19]

Additional predictors of opioid discharge prescription	
Length of stay	Following cardiac surgery, longer length of hospital stay was associated with opioid-free discharge.[20]
In-hospital opioid consumption	In-hospital opioid consumption was associated with post-discharge opioid consumption following caesarean delivery.[6,21]
Discharge prescription included NSAIDs	ERAS Society guidelines recommend multimodal postoperative analgesia including acetaminophen and NSAIDs following caesarean delivery.[17]
Preprinted prescription form with 10 vs. 20 morphine pills	Larger discharge prescriptions of opioids were associated with increased post-discharge opioid consumption following caesarean delivery.[21,22]

ASA: American Society of Anaesthesiologists, EPDS: Edinburgh Postnatal Depression Scale, NSAIDs: nonsteroidal anti-inflammatory drugs, POD: postoperative day, PACU: post-anesthesia care unit, ERAS: Enhance Recovery After Surgery.

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Table S4: Univariate analysis of predictors of in-hospital opioid consumption (N=904)

Predictor	IRR [95% CI]	p-value
Age (older)	1.023 [1.007 to 1.039]	**0.004**
ASA Score > 2	2.997 [2.401 to 3.739]	**< 0.001**
Smoking during pregnancy (vs. not)	4.029 [2.794 to 5.811]	**< 0.001**
Previous caesarean (vs. none)	0.594 [0.503 to 0.701]	**< 0.001**
Multiple gestation (vs. single fetus)	1.611 [1.149 to 2.259]	**0.006**
Pregnancy complications (vs. none)	1.247 [1.060 to 1.468]	**0.008**
Mental Health Disorder (vs. none)	2.540 [1.983 to 3.254]	**< 0.001**
Edinburgh Postnatal Depression Score (higher)	1.074 [1.051 to 1.097]	**< 0.001**
Opioid use during pregnancy (vs. none)	34.203 [12.681 to 92.250]	**< 0.001**
Received NSAIDs in hospital (vs. none)	0.426 [0.330 to 0.551]	**< 0.001**
Labor before caesarean (vs. not)	1.486 [1.264 to 1.748]	**< 0.001**
Emergency (vs. elective)	2.031 [1.724 to 2.934]	**< 0.001**
Surgery duration (longer)	1.007 [1.002 to 1.012]	**0.008**
Concomitant procedures (vs. only caesarean)	1.348 [1.071 to 1.696]	**0.011**
Intraoperative or inpatient complications (vs. none)	1.185 [0.993 to 1.415]	0.060
Highest pain score POD0-2	1.706 [1.629 to 1.785]	**< 0.001**
PACU opioid consumption in MME (higher)	1.034 [1.028 to 1.039]	**< 0.001**

Negative binomial regression with multiple imputations. IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Table S5: Complete regression model – Negative Binomial Regression, Multiple Imputations, Before stepwise selection (N=904)

Predictor	Coefficient [95% CI]	p-value
Age (older)	1.014 [0.994 to 1.004]	0.175
ASA Score > 2	1.152 [0.873 to 1.520]	0.317
Smoking during pregnancy (vs. not)	1.006 [0.592 to 1.709]	0.983
Previous caesarean (vs. none)	0.966 [0.769 to 1.172]	0.768
Multiple gestation (vs. single fetus)	1.078 [0.728 to 1.594]	0.709
Pregnancy complications (vs. none)	0.946 [0.765 to 1.170]	0.607
Mental Health Disorder (vs. none)	1.124 [0.808 to 1.563]	0.488
Edinburgh Postnatal Depression Score (higher)	1.008 [0.982 to 1.034]	0.568
Opioid use during pregnancy (vs. none)	8.009 [2.681 to 23.922]	**< 0.001**
Received NSAIDs in hospital (vs. none)	0.647 [0.475 to 0.882]	**0.006**
Labor before caesarean (vs. not)	0.923 [0.718 to 1.188]	0.568
Emergency (vs. elective)	1.263 [0.958 to 1.665]	0.098
Surgery duration (longer)	1.004 [0.998 to 1.011]	0.190
Concomitant procedures (vs. only caesarean)	1.057 [0.785 to 1.422]	0.716
Intraoperative or inpatient complications (vs. none)	0.970 [0.782 to 1.204]	0.785
Highest pain score POD0-2	1.584 [1.508 to 1.664]	**< 0.001**
PACU opioid consumption in MME (higher)	1.007 [1.002 to 1.013]	**0.010**

Negative binomial regression with multiple imputations. CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day, PACU: post-anesthesia care unit, MME: milligram morphine equivalents.

Table S6: Final regression model (Sensitivity Analysis 1 – No Imputations), After Stepwise Selection (N= 727)

Predictor	IRR [95% CI]	p-value
Opioid use during pregnancy (vs. no use)	13.270 [4.140 to 42.542]	**< 0.001**
Emergency (vs. elective)	1.283 [1.030 to 1.600]	**0.026**
Concomitant procedure (vs. only caesarean)	1.275 [0.946 to 1.717]	0.110
Received NSAIDs (vs. no NSAIDs)	0.536 [0.377 to 0.761]	**< 0.001**
Highest pain score POD0-2	1.596 [1.514 to 1.682]	**< 0.001**

Negative binomial regression. IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: Post-Operative Day.

Table S7: Complete regression model (Sensitivity Analysis 1 – No Imputations), Before Stepwise Selection (N=727)

Predictor	IRR [95% CI]	p-value
Age (older)	1.010 [0.988 to 1.033]	0.389
ASA Score > 2	1.087 [0.787 to 1.501]	0.613
Smoking during pregnancy (vs. not)	1.022 [0.579 to 1.805]	0.940
Previous caesarean (vs. none)	1.002 [0.777 to 1.293]	0.988
Multiple gestation (vs. single fetus)	1.013 [0.629 to 1.632]	0.958
Pregnancy complications (vs. none)	0.894 [0.703 to 1.137]	0.361
Mental Health Disorder (vs. none)	1.117 [0.787 to 1.585]	0.537
Edinburgh Postnatal Depression Score (higher)	1.007 [0.980 to 1.034]	0.617
Opioid use during pregnancy (vs. none)	10.294 [2.889 to 36.682]	**< 0.001**
Received NSAIDs in hospital (vs. none)	0.562 [0.382 to 0.825]	**0.003**
Labor before caesarean (vs. not)	0.840 [0.634 to 1.115]	0.228
Emergency (vs. elective)	1.436 [1.075 to 1.957]	**0.022**
Surgery duration (longer)	1.002 [0.995 to 1.010]	0.596
Concomitant procedures (vs. only caesarean)	1.225 [0.877 to 1.710]	0.234
Intraoperative or inpatient complications (vs. none)	0.987 [0.774 to 1.258]	0.914
Highest pain score POD0-2	1.585 [1.500 to 1.675]	**< 0.001**
PACU opioid consumption in MME (higher)	1.003 [0.996 to 1.009]	0.385

Negative binomial regression. IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: Post-Operative Day, PACU: Post-Anesthesia Care Unit, MME: Milligram Morphine Equivalents.

Table S8: Final regression model (Sensitivity Analysis 4 – Outliers [>50 MME/day] removed) Multiple imputations, After stepwise selection (N=884)

Predictor	IRR [95% CI]	p-value
Opioid use during pregnancy (vs. none)	6.936 [2.072 to 23.213]	**0.002**
Received NSAIDs in hospital (vs. none)	0.533 [0.395 to 0.718]	**< 0.001**
Highest pain score POD0-2	1.566 [1.491 to 1.644]	**< 0.001**

Negative binomial regression with multiple imputations. MME: Milligram Morphine Equivalents, IRR: Incidence Rate Ratio, CI: Confidence Interval, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day.

Table S9: Complete regression model (Sensitivity Analysis 4 – Outliers [>50 MME/day] removed) Multiple imputations, Before stepwise selection (N=884)

Predictor	IRR [95% CI]	p-value
Age (higher)	0.999 [0.978 to 1.021]	0.951
ASA Score > 2	1.159 [0.864 to 1.554]	0.325
Smoking during pregnancy (vs. not)	1.011 [0.570 to 1.795]	0.970
Previous caesarean (vs. none)	1.006 [0.789 to 1.281]	0.964
Multiple gestation (vs. single fetus)	0.999 [0.642 to 1.554]	0.995
Pregnancy complications (vs. none)	0.908 [0.729 to 1.132]	0.391
Mental Health Disorder (vs. none)	1.172 [0.830 to 1.658]	0.368
Edinburgh Postnatal Depression Score (higher)	1.012 [0.985 to 1.039]	0.386
Opioid use during pregnancy (vs. none)	4.805 [1.395 to 16.545]	**0.013**
Received NSAIDs in hospital (vs. none)	0.574 [0.414 to 0.795]	**0.001**
Labor before caesarean (vs. not)	0.917 [0.708 to 1.188]	0.512
Emergency (vs. elective)	1.152 [0.869 to 1.527]	0.325
Surgery duration (vs. longer)	1.001 [0.994 to 1.007]	0.892
Concomitant procedures (vs. only caesarean)	0.811 [0.584 to 1.128]	0.214
Intraoperative or inpatient complications (vs. none)	1.133 [0.901 to 1.426]	0.286
Highest pain score POD0-2	1.548 [1.471 to 1.629]	**< 0.001**
PACU opioid consumption in MME (higher)	1.004 [0.996 to 1.013]	0.325

Negative binomial regression with multiple imputations. MME: Milligram Morphine Equivalents, IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day, PACU: post-anesthesia care unit, MME: milligram morphine equivalents.

Table S10: Final regression model (Sensitivity Analysis 2 – MME Consumed during full length of stay) Multiple imputations, After stepwise selection (N=904)

Predictor	IRR [95% CI]	p-value
Age (older)	1.016 [0.998 to 1.034]	0.090
Opioid use during pregnancy (vs. none)	10.803 [3.946 to 29.581]	**< 0.001**
Received NSAIDs in hospital (vs. none)	0.573 [0.430 to 0.764]	**< 0.001**
Emergency (vs. elective)	1.210 [0.993 to 1.475]	0.059
Highest pain score POD0-2	1.600 [1.525 to 1.679]	**< 0.001**
PACU opioid consumption in MME (higher)	1.009 [1.004 to 1.014]	**0.001**

Negative binomial regression with multiple imputations. MME: Milligram Morphine Equivalents, IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day, PACU: post-anesthesia care unit, MME: milligram morphine equivalents.

Table S11: Complete regression model (Sensitivity Analysis 2 – MME Consumed during full length of stay) Multiple imputations, Before stepwise selection (N=904)

Predictor	IRR [95% CI]	p-value
Age (higher)	1.016 [0.997 to 1.036]	0.103
ASA Score > 2	1.214 [0.921 to 1.600]	0.169
Smoking during pregnancy (vs. not)	1.015 [0.573 to 1.796]	0.961
Previous caesarean (vs. none)	0.960 [0.763 to 1.108]	0.727
Multiple gestation (vs. single fetus)	1.278 [0.871 to 1.875]	0.210
Pregnancy complications (vs. none)	0.928 [0.752 to 1.146]	0.488
Mental Health Disorder (vs. none)	1.069 [0.770 to 1.485]	0.690
Edinburgh Postnatal Depression Score (higher)	1.010 [0.984 to 1.037]	0.465
Opioid use during pregnancy (vs. none)	9.125 [3.006 to 27.700]	**< 0.001**
Received NSAIDs in hospital (vs. none)	0.637 [0.468 to 0.869]	**0.004**
Labor before caesarean (vs. not)	0.899 [0.699 to 1.156]	0.405
Emergency (vs. elective)	1.285 [0.976 to 1.692]	0.074
Surgery duration (vs. longer)	1.005 [0.998 to 1.011]	0.183
Concomitant procedures (vs. only caesarean)	1.034 [0.770 to 1.390]	0.822
Intraoperative or inpatient complications (vs. none)	1.057 [0.853 to 1.308]	0.613
Highest pain score POD0-2	1.589 [1.513 to 1.667]	**< 0.001**
PACU opioid consumption in MME (higher)	1.008 [1.002 to 1.013]	**0.005**

Negative binomial regression with multiple imputations. MME: Milligram Morphine Equivalents, IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day, PACU: post-anesthesia care unit, MME: milligram morphine equivalents.

Table S12: Univariate analysis of predictors of opioids prescribed at discharge (N=876)

Predictor	IRR [95% CI]	p-value
Age (older)	0.993 [0.980 to 1.006]	0.299
ASA Score > 2	1.031 [0.843 to 1.261]	0.769
Smoking during pregnancy (vs. not)	1.124 [0.798 to 1.585]	0.503
Previous caesarean (vs. none)	0.981 [0.855 to 1.125]	0.780
Multiple gestation (vs. single fetus)	0.939 [0.690 to 1.279]	0.690
Pregnancy complications (vs. none)	0.994 [0.866 to 1.141]	0.932
Mental Health Disorder (vs. none)	1.037 [0.828 to 1.298]	0.755
Edinburgh Postnatal Depression Score (higher)	1.007 [0.991 to 1.024]	0.370
Opioid use during pregnancy (vs. none)	1.084 [0.396 to 2.971]	0.875
Received NSAIDs in hospital (vs. none)	0.949 [0.761 to 1.184]	0.642
Labor before caesarean (vs. not)	1.080 [0.942 to 1.237]	0.271
Emergency (vs. elective)	1.036 [0.902 to 1.190]	0.616
Surgery duration (longer)	1.000 [0.995 to 1.004]	0.810
Concomitant procedures (vs. only caesarean)	0.889 [0.727 to 1.086]	0.249
Intraoperative or inpatient complications (vs. none)	0.971 [0.835 to 1.130]	0.705
Highest pain score POD0-2	1.012 [0.987 to 1.038]	0.334
Length of stay (longer)	0.960 [0.866 to 1.065]	0.441
Discharge prescription included NSAIDs (vs. none)	1.021 [0.785 to 1.329]	0.876
Inpatient opioid consumption (higher)	1.003 [0.994 to 1.011]	0.546
Preprinted prescription form with 10 morphine tablets (vs. 20 tablets)	0.548 [0.389 to 0.770]	**0.001**

Negative binomial regression with multiple imputations. IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

Table S13: Opioid pills at discharge, Complete regression model – Negative Binomial Regression, Multiple Imputations, Before stepwise selection (N=876)

Predictor	IRR [95% CI]	p-value
Age (older)	0.995 [0.981 to 1.009]	0.509
ASA Score > 2	1.024 [0.820 to 1.278]	0.835
Smoking during pregnancy (vs. not)	1.106 [0.769 to 1.592]	0.587
Previous caesarean (vs. none)	1.043 [0.880 to 1.236]	0.626
Multiple gestation (vs. single fetus)	1.034 [0.747 to 1.419]	0.883
Pregnancy complications (vs. none)	1.009 [0.871 to 1.170]	0.902
Mental Health Disorder (vs. none)	0.974 [0.771 to 1.231]	0.827
Edinburgh Postnatal Depression Score (higher)	1.006 [0.989 to 1.023]	0.477
Opioid use during pregnancy (vs. none)	0.782 [0.225 to 2.721]	0.699
Received NSAIDs in hospital (vs. none)	0.957 [0.731 to 1.253]	0.748
Labor before caesarean (vs. not)	1.095 [0.920 to 1.303]	0.306
Emergency (vs. elective)	0.982 [0.807 to 1.195]	0.856
Surgery duration (longer)	1.000 [0.996 to 1.005]	0.980
Concomitant procedures (vs. only caesarean)	0.914 [0.735 to 1.136]	0.417
Intraoperative or inpatient complications (vs. none)	0.967 [0.827 to 1.130]	0.674
Highest pain score POD0-2	1.015 [0.988 to 1.043]	0.291
Length of stay (longer)	0.944 [0.841 to 1.061]	0.333
Discharge prescription included NSAIDs (vs. none)	1.054 [0.769 to 1.444]	0.743
Inpatient opioid consumption (higher)	1.003 [0.992 to 1.014]	0.605
Preprinted prescription form with 10 morphine tablets (vs. 20 tablets)	0.559 [0.395 to 0.791]	**0.001**

Negative binomial regression with multiple imputations. MME: Milligram Morphine Equivalents, IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day.

Table S14: Opioid pills at discharge, Final regression model (Sensitivity Analysis 1 – No Imputations) After stepwise Selection (N=708)

Predictor	IRR [95% CI]	p-value
No significant predictors identified		

Negative binomial regression. IRR: Incidence Rate Ratio, CI: Confidence Interval.

Table S15: Opioid pills at discharge, Complete regression model (Sensitivity Analysis 1 – No Imputations) Before stepwise Selection (N=708)

Predictor	IRR [95% CI]	p-value
Age (older)	0.996 [0.980 to 1.011]	0.577
ASA Score > 2	1.021 [0.798 to 1.308]	0.867
Smoking during pregnancy (vs. not)	1.107 [0.744 to 1.165]	0.617
Previous caesarean (vs. none)	1.055 [0.875 to 1.272]	0.575
Multiple gestation (vs. single fetus)	1.073 [0.735 to 1.566]	0.716
Pregnancy complications (vs. none)	1.004 [0.851 to 1.185]	0.964
Mental Health Disorder (vs. none)	0.993 [0.776 to 1.270]	0.953
Edinburgh Postnatal Depression Score (higher)	1.006 [0.988 to 1.025]	0.521
Opioid use during pregnancy (vs. none)	0.668 [0.126 to 3.529]	0.634
Received NSAIDs in hospital (vs. none)	1.040 [0.767 to 1.410]	0.801
Labor before caesarean (vs. not)	1.094 [0.898 to 1.333]	0.372
Emergency (vs. elective)	0.988 [0.797 to 1.140]	0.917
Surgery duration (longer)	0.999 [0.994 to 1.004]	0.753
Concomitant procedures (vs. only caesarean	0.895 [0.703 to 1.140]	0.368
Intraoperative or inpatient complications (vs. none)	0.956 [0.805 to 1.136]	0.610
Highest pain score POD0-2	1.021 [0.991 to 1.052]	0.179
Length of stay (longer)	0.940 [0.825 to 1.071]	0.350
Discharge prescription included NSAIDs (vs. none)	0.994 [0.687 to 1.437]	0.972
Inpatient opioid consumption (higher)	1.003 [0.991 to 1.015]	0.650
Preprinted prescription form with 10 morphine tablets (vs. 20 tablets)	0.568 [0.388 to 0.832]	**0.004**

Negative binomial regression. IRR: Incidence Rate Ratio, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day.

Table S16: Opioid pills at discharge, Final regression model (Sensitivity Analysis 2 – Without Outliers [>50 MME/day] removed) After stepwise Selection (N=830)

Predictor	IRR [95% CI]	p-value
Preprinted prescription form with 10 morphine tablets (vs. 20 tablets)	0.547 [0.383 to 0.780]	**0.001**

Negative binomial regression with multiple imputations. MME: Milligram Morphine Equivalents, IRR: Incidence Rate Ratio, CI: Confidence Interval.

Table S17: Opioid pills at discharge, Complete regression model (Sensitivity Analysis 2 – Without Outliers [>50 MME/day] removed) Before stepwise Selection (N=830)

Predictor	IRR [95% CI]	p-value
Age (older)	0.996 [0.982 to 1.011]	0.624
ASA Score > 2	0.991 [0.788 to 1.246]	0.937
Smoking during pregnancy (vs. not)	1.087 [0.743 to 1.590]	0.669
Previous caesarean (vs. none)	1.017 [0.855 to 1.211]	0.849
Multiple gestation (vs. single fetus)	1.037 [0.734 to 1.465]	0.836
Pregnancy complications (vs. none)	1.025 [0.881 to 1.192]	0.752
Mental Health Disorder (vs. none)	0.959 [0.752 to 1.222]	0.733
Edinburgh Postnatal Depression Score (higher)	1.006 [0.989 to 1.024]	0.491
Opioid use during pregnancy (vs. none)	0.681 [0.205 to 2.265]	0.531
Received NSAIDs in hospital (vs. none)	0.977 [0.738 to 1.292]	0.869
Labor before caesarean (vs. not)	1.094 [0.915 to 1.308]	0.325
Emergency (vs. elective)	0.967 [0.790 to 1.183]	0.742
Surgery duration (longer)	1.000 [0.996 to 1.005]	0.873
Concomitant procedures (vs. only caesarean	0.949 [0.758 to 1.188]	0.647
Intraoperative or inpatient complications (vs. none)	0.975 [0.830 to 1.146]	0.760
Highest pain score POD0-2	1.013 [0.981 to 1.045]	0.434
Length of stay (longer)	0.938 [0.830 to 1.060]	0.305
Discharge prescription included NSAIDs (vs. none)	1.092 [0.791 to 1.506]	0.593
Inpatient opioid consumption (higher)	1.014 [0.974 to 1.055]	0.507
Preprinted prescription form with 10 morphine tablets (vs. 20 tablets)	0.554 [0.386 to 0.795]	**0.001**

Negative binomial regression with multiple imputations. MME: Milligram Morphine Equivalents, CI: Confidence Interval, ASA: American Society of Anesthesiologists, NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, POD: postoperative day.

Table S18: Postoperative outcomes among in-hospital opioid consumers and non-consumers (N=904)

Outcome	**Opioid consumers** (N=410)	**Opioid non-consumers** (N=494)	**p-value**
Length of stay (days) *	2.4 ± 1.0	2.1 ± 0.5	**<0.001**
In-hospital PONV †	115 (28.1%)	97 (19.6%)	**0.003**
30-Day Postoperative Complications (excluding PONV) †	54 (13.2%)	35 (7.1%)	**0.002**
30-day Readmission ‡	10 (2.4%)	3 (0.6%)	**0.025**
30-day Emergency Department Visit ‡	5 (1.2%)	6 (1.2%)	0.613

*Data are reported as frequency n (%) or mean ± SD. PONV: postoperative nausea/vomiting, SD: standard deviation. *Mann Whitney U test. †Chi-squared test. ‡Fisher exact test.*