IDENTIFYING DISTINCT TRAJECTORIES OF ACUTE POST-SURGICAL PAIN AND THEIR ASSOCIATIONS WITH PERSISTENT POST-SURGICAL PAIN, OPIOID USE, AND 30-DAY READMISSION AFTER ABDOMINAL HYSTERECTOMY FOR GYNECOLOGIC CANCER

by

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Background: Acute post-surgical pain (APSP) following hysterectomy is a critical concern, especially in the context of gynecologic cancer. APSP often extends hospital stays and increases medical costs and may evolve into chronic pain if not adequately managed. Despite its dynamic nature, APSP is frequently operationalized as a static variable, leading to a gap in research regarding its trajectories and long-term implications post-hysterectomy.

Purpose: (1) determine distinct APSP trajectories over five days post-hysterectomy in gynecologic cancer patients; (2) analyze factors associated with these pain trajectories; and (3) explore the associations between APSP trajectories and postoperative outcomes, including 30-day readmission, persistent postsurgical pain, and prolonged opioid usage, with a particular focus on high-risk gynecologic cancer cases.

Methods: Utilizing a large Enhanced Recovery After Surgery (ERAS) dataset and medical records, the study examined adult patients undergoing abdominal hysterectomy from 2019 to 2021. It included 1342 gynecologic cancer patients, with 407 having high-risk cancers and receiving chemotherapy. Group-based trajectory modeling identified APSP patterns, and multinomial regression analyzed associated factors. High-risk endometrial and ovarian cancer patients were separately studied to link APSP trajectories to postoperative outcomes.

Results: Four APSP trajectories were found: no pain, rapid resolution, slow resolution, and ongoing pain. Factors like prior anxiety, preoperative pelvic pain, open hysterectomy, and higher ASA Class increased ongoing pain likelihood. Higher CCI scores and longer surgeries correlated with less chance of no or rapid pain resolution. In high-risk patients, three trajectories were noted. Ongoing pain trajectory was a significant predictor for persistent post-hysterectomy pain and 30-day readmission.

Conclusions This investigation illuminates the incidence of ongoing APSP in gynecologic cancer patients. The distinct pain trajectories identified are instrumental for tailoring postoperative pain management. Recognizing these patterns is pivotal for healthcare providers to deploy targeted interventions that mitigate chronic pain and reduce opioid dependency, optimizing recovery after hysterectomy.

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Preface

This dissertation stands as a testament to the collaborative efforts and support I received from the Enhanced Recovery After Surgery (ERAS) program at Magee Women's Hospital, which generously granted me access to an invaluable dataset, thereby catalyzing my research journey.

I am deeply thankful for my committee members, whose advice has been a guiding light throughout this academic journey. A special thanks to Dr. Heidi Donovan, my committee chair, whose endless dedication, and kindness have guided me from the beginning to the end. You've sparked in me a love for nursing research that I hope to pass on to others. The knowledge you've given me will influence my future work. Dr. Susan Sereika, your tailored support through the data analysis was pivotal. The knowledge I gleaned from your statistics course laid the groundwork for this dissertation, bestowing upon me skills that I will cherish and utilize lifelong. Dr. Sarah M. Belcher, our interactions may have been scant in the physical realm, but I have been deeply connected with your intellect and work. Your exemplary past contributions have been a guiding light in both my comprehensive exams and the drafting of this dissertation. Your suggestions and meticulous attention to writing details have enriched my academic fabric, but most importantly, you've modeled an unwavering professionalism and dedication to research. Dr. Sarah E. Taylor, without your initial assistance, this study might never have commenced. Your aid in data collection, along with your ongoing clinical expertise, were indispensable. Dr. Susan W. Wesmiller, your research has been incredibly inspiring to me, and I'm so grateful for your openness in sharing the process of recruiting participants. You handle nursing research with a kind but firm touch, showing what it means to be strong and determined. I have great respect for the example you set.

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1.0 PROPOSAL INTRODUCTION

1.1 SPECIFIC AIMS

Chronic postsurgical pain (CPSP), defined as pain that develops after a surgical procedure and persists beyond the healing period, typically for at least two to three months, is a common problem after hysterectomy for gynecologic cancer and can have a major impact on function and quality of life. In 2022, an estimated 66,570 people in the United States will be diagnosed with uterine, or endometrial cancer. An estimated 14,480 will be diagnosed with invasive cervical cancer, and an estimated 21,410 people will be diagnosed with ovarian, fallopian tube, and peritoneal cancer. Hysterectomy, or surgical removal of the uterus, is commonly used in the treatment of gynecologic cancers, and many patients experience acute postsurgical pain (APSP) that usually resolves within 1 weeks. However, CPSP can develop after acute postsurgical pain (APSP), irrespective of surgical success, in 12%-50% of patients undergoing hysterectomy (Brandsborg et al., 2007; Honerlaw et al., 2016a). Although CPSP after hysterectomy is usually mild (<=3 out of a 0-10 numerical rating scale for pain) (Brandsborg & Nikolajsen, 2018a), CPSP can interfere with daily living activities, work, and social function, and negatively affect quality of life (Sheng et al., 2017). CPSP can also result in significant medical and socioeconomic problems for gynecological cancer survivors such as emotional distress and healthcare utilization (Sng et al., 2018b). Therefore, it is urgent to better understand and prevent CPSP in patients after gynecological cancer surgery to decrease the negative impact on their future physical and psychological well-being.

A range of sociodemographic/lifestyle factors, psychological, medical history, and perioperative factors have been evaluated for their influence on the development of severe APSP and CPSP following a hysterectomy, but controversies remain.

Sociodemographic/lifestyle factors: Age and body mass index (BMI) are prominently highlighted in postsurgical pain research. Studies such as those by van Ransbeeck et al. (2018) and Wang et al. (2018) show that younger patients typically report greater APSP intensity. On the other hand, some research, like the findings of Won et al. (2018), shows no significant correlation between age and APSP. The relationship between BMI and APSP presents a U-shaped curve. Specifically, women at the extremes, either with a BMI of 30 or above or 20 or below, are at a heightened risk of APSP (Osler et al., 2011). Other factors meriting attention include preoperative smoking status, education level, and race. However, comprehensive research on these factors, especially in the context of hysterectomy, remains scarce (Jin et al., 2020; Sng et al., 2018b). Age is also highlighted in CPSP research. For example, in a retrospective analysis of 1135 patients with CPSP after hysterectomy, Brandsborg et al found that age was not associated with pain (Brandsborg, 2012), while a cohort study of 2929 patients found that age <51 years was a risk factor for the development of CPSP (Montes et al., 2015a). Other sociodemographic factors, such as education level, cancer stage, and race have been studied in CPSP, but the sample size and number of studies examining the same factors are limited, and studies of CPSP after cancer-related hysterectomy are rare.

Psychological Factors: The intersection of psychology and postsurgical pain predominantly revolves around anxiety, depression, and pain catastrophizing. The role of anxiety is particularly noteworthy due to its potential to influence pain perception through descending pathways (Tseng

et al., 2017; van Boekel et al., 2021). Previous findings also suggest that trait anxiety affects postsurgical pain by influencing presurgical state anxiety (Kain et al., 2000).

Medical History Factors: Several aspects of a patient's medical history can be predictive of APSP and CPSP. Notable among these could be specific diagnosis, the stage of cancer, the Charlson Comorbidity Index (CCI), and any record of previous pelvic or abdominal surgeries (e.g., history of abdominal surgery, history of cesarean section) (Brandsborg, 2012; Pinto et al., 2012).

Perioperative Factors: The state of a patient's pain before the surgery and their history with opioids can be indicative of their post-surgical pain experience. Those with preoperative pain or a history of opioid use frequently report higher APSP scores (Menendez et al., 2018). The use of opioid pharmacotherapy before surgery and severe APSP has also been proven to be associated with higher level of CPSP (Chapman, Davis, et al., 2011). The nature of the surgical procedure itself can also be a determinant, as different surgeries involve varying levels of tissue trauma, nerve damage, and inflammatory responses. However, the relationship between surgical procedure and postoperative pain, specifically after abdominal hysterectomies, remains under debate. In a prospective study, Pinto et al. indicated that abdominal hysterectomy (median incision and Pfannenstiel incision) was a predictor of CPSP after hysterectomy (Pinto et al., 2018a), however Brandsborg et al. (2007) did not find differences in the incidence of CPSP after different hysterectomy surgical methods. Given the typically traumatic nature of extended, cancer-related surgeries, further studies are crucial to fully understand the interplay between surgical related factors such as surgery procedure/duration, and postoperative pain.

APSP and CPSP have rarely been studied in the context of gynecologic cancer. Importantly, although some studies have investigated the incidence and risk factors of CPSP following hysterectomy for benign indications, little is known about the characteristics that put patients with

gynecological cancer at risk for CPSP after hysterectomy. The extent of surgery (surgery duration, sub-total vs total hysterectomy, surgical staging procedures) and chemotherapy have an influence on postoperative pain(Pecorino et al., 2022). In addition, the psychological stress of surgery and diagnosis is likely to be worse in patients with gynecological cancer compared to benign tumors and could also impact development of CPSP. Therefore, to address gaps in the literature, this study proposes to evaluate APSP and CPSP risk factors more comprehensively among patients after hysterectomy for a gynecological cancer(Honerlaw et al., 2016b; Weinrib et al., 2017). Finally, poorly controlled APSP is one of the strongest predictors of the development of CPSP, but the interacting influences of pain severity and opioid use for pain management on CPSP is not fully understood.

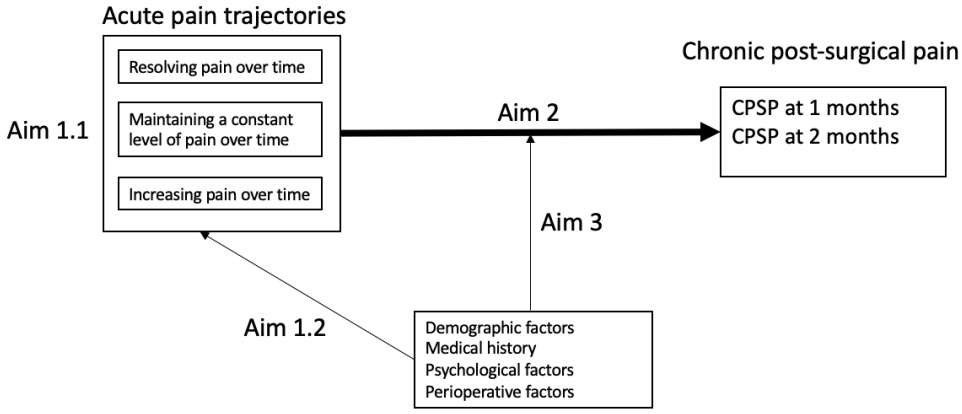
Evaluating trajectories of acute pain resolution could provide novel insights into the development of CPSP(Chapman et al., 2011a). Studies investigating the transition from APSP to CPSP often focus on the patient's pain intensity levels during the immediate postoperative period, typically within 48 to 72 hours after surgery. Commonly, this data is collected using a numerical rating scale (NRS), where patients rate their pain from 0 (no pain) to 10 (worst possible pain). However, this approach may not provide a complete understanding of the pain's trajectory. To thoroughly evaluate the influence of APSP on the development of CPSP, it is essential to consider not only the pain intensity but also the subsequent rate at which pain resolves following surgery. We hypothesize that the resolution rate of acute pain post-surgery is a critical and clinically significant predictor for the onset of CPSP. This hypothesis is grounded in the idea that a slower diminishment of pain could be indicative of underlying pathophysiological processes, such as prolonged inflammation, which could make patients to chronic pain states (Voscopoulos & Lema, 2010). Previous studies have shown that patients with higher pain scores postoperatively, or those

who experience pain for an extended period, are at increased risk for long-term pain(Hinrichs-Rocker et al., 2009; Imai et al., 2021).

A trajectory modeling approach to the classification of APSP measurement permits classification of patients into categories such as: 1) resolving pain over time; 2) maintaining a constant level of pain over time; or 3) increasing pain intensity over time(Okamoto et al., 2018). However, the classification of acute pain trajectories has rarely been linked with the development of chronic pain in patients with gynecological cancer. Acute postoperative pain not only can develop into a chronic affliction, but also can extend a patient's hospital stay and amplifying medical expenses (Gan, 2017). Moreover, the unsolved APSP could led to an increase in opioid prescriptions postoperatively. While opioids can be effective in alleviating intense pain in the immediate post-surgical phase, their prolonged use could pose significant risks such as opioid dependence and addiction. When prolonged opioid use is integrated with chemotherapy, it can significantly compromise the overall well-being of patients and adversely affect treatment outcomes. This is due to heightened risks like exacerbated gastrointestinal issues, increased susceptibility to infections from a weakened immune system, and the compounding effects of cognitive impairments and mood disorders(Grp et al., 2020; Rosenthal et al., 2019). Previous studies have established some understanding of the long-term effects of APSP(Hinrichs-Rocker et al., 2009). However, the dynamic trajectory of APSP and its long-term implications after hysterectomy still warrant further exploration.

In summary, addressing the critical gaps in research on APSP and CPSP in gynecologic cancer, the first step is to ascertain whether distinct categories of patients exist based on their pain trajectories post-hysterectomy. Following this, it is essential to investigate the upstream factors

that predispose patients to fall into these distinct groups, as well as the downstream health consequences such as CPSP associated with each group. The current weaknesses in this domain of research are evidenced by 1) a neglect in characterizing and understanding the progression of acute pain following hysterectomy; 2) the obscurity surrounding the determinants of APSP and CPSP following hysterectomy; 3) the dearth of targeted research on patients with gynecologic cancer, who may face a greater incidence of postsurgical pain in comparison to those with benign conditions; 4) unexplored dynamic trajectory of APSP and its long-term implications after hysterectomy. This conceptual framework of this study is presented in **Figure 1**. Robust literature in CPSP and APSP supports the premise that identification of characteristics of patients after hysterectomy most at risk for CPSP will prevent CPSP through early risk identification and interruption of the transition from APSP to CPSP pathways. Our central hypothesis is that trajectories of acute pain are significant predictors of CPSP whereby individuals who don't experience a resolution or have increases in pain over the post-operative period will be at higher risk for development of post-hysterectomy chronic pain.



1 Figure 1 The conceptual framework of the proposed study

This study will leverage an existing Enhanced Recovery After Surgery (ERAS) dataset that captures detailed pain ratings through postsurgical day0 to day5. The combined dataset encompassed demographic details, medical comorbidities, pathologic findings, surgical techniques, and postoperative pain experiences for patients who underwent abdominal hysterectomy. This ancillary study of an existing large dataset of patients enrolled in an ERAS protocol dataset will allow us to answer the following aims in a sample of adult (>18) patients with gynecologic cancer who underwent abdominal hysterectomy. All patients with surgery between January 1st ,2019 and December 31st, 2021, who meet inclusion criteria will be included in the analysis. This period from 2019 to late 2021 allows for the assessment of recent and relevant clinical practices and patient outcomes, at the same time provide a sufficient timeframe to accumulate a robust sample size for the analysis.

Aim 1: Determine distinct post-operative acute pain trajectories over 5 days following hysterectomy for a gynecological cancer, and evaluate factors associated with trajectory membership.

- Aim 1.1 The study proposes to use group-based trajectory models to generate acute pain trajectories. The fit estimates both pain intensity and rate of pain resolution, thus increasing the information that pain assessment provides and giving us a more comprehensive understanding of different trajectories of APSP.
- Aim 1.2 To identify determinants of acute pain trajectories, multinomial regression models will be constructed to determine associations between baseline factors (demographic factors, medical factors, and surgery related factors) and trajectories of acute pain with adjustment for potential confounders.

Aim 2: Examine the relationships between acute pain trajectories and the development of chronic pain.

- Predictive value of the acute pain trajectory for the presence of pain at 1 and 2 months after surgery will be assessed using logistic regression analyses for each timepoint.

Exploratory Aim3: Explore whether patient-related factors and medical characteristics moderate the relationship between acute pain trajectories and chronic pain.

- A multivariate regression approach will be conducted to examine whether risk factors for CPSP (age, surgical methods, and perioperative opioid use) moderate the relationship between acute pain trajectories and CPSP at 1 month and 2 months.

My long-term goal is to develop targeted interventions to prevent CPSP among patients undergoing hysterectomy for gynecological cancer, especially for those at high risk for unresolved APSP trajectory. The proposed objectives of this dissertation study are the first steps in developing this program of research. The focus on different trajectories of acute pain resolution (or non-resolution) and their association with CPSP development is innovative. Risk factors like age, surgical procedures, and opioid use that remain debated or unexplored are also considered in this study. By identifying characteristics of patients at high risk for unresolved APSP and CPSP, findings from this study will provide the basis for future research that will include development of targeted pain management interventions, and interventions to trigger appropriate screening of CPSP in high-risk patients with gynecologic cancer.

1.2 BACKGROUND, SIGNIFICANCE, AND INNOVATION

1.2.1 Background

1.2.1.1 Acute postsurgical pain (APSP)

Definition and mechanism of APSP

Acute pain is an unpleasant, complex, dynamic psychophysiological response caused by activation of high threshold nociceptors. Normally, acute pain is self-limiting and confined to a given period after tissue trauma or acute inflammatory processes(Chapman & Vierck, 2017). Acute postsurgical pain mainly includes acute trauma (somatic pain or incision pain) or damage to internal organs (visceral pain) caused by surgical operations, as well as pain caused by inflammatory stimulation around nerve endings, which belongs to nociceptive pain(Brandsborg, 2012a).

Consequences of APSP after hysterectomy

Acute postoperative pain can prolong the patient's hospital stay, increase the patient's medical expenses, and is also closely related to serious postoperative complications such as cardiovascular diseases and thrombosis-related diseases(Gan, 2017). Hysterectomy that accompanies acute pain, if uncontrolled, can develop into chronic pain and exert deleterious influences on health. For example, a study by Theunissen (2016) found high rates of acute postoperative pain in patients undergoing hysterectomy. Among those with moderate to severe acute pain (usually defined as NRS>3 on a 0-10 scale), 10%-50% patients developed post-surgical chronic pain(Brandsborg et al., 2009; Katz & Seltzer, 2009; Theunissen et al., 2016; VanDenKerkhof et al., 2012)

Risk factors for APSP

Sociodemographic/lifestyle factors (e.g., age, gender, smoking) are the most common factors evaluated for their association with APSP (Yang et al., 2019). Several studies have shown that younger patients report higher APSP intensity (van Ransbeeck et al., 2018; Wang et al., 2018). One study suggested that age is not correlated with postoperative acute pain intensity(Won et al., 2018), but this was a small sample study with low statistical power. Body mass index (BMI) is also positively related to APSP with a U -shape association. Women BMI>=30 and BMI<=20 have a higher possibility to develop APSP(Osler et al., 2011). Patients who smoked preoperatively had greater pain intensity at 3 days postoperatively and had higher needs for opioids(Chowdhury et al., 2019). Other demographic factors, such as education level, race, etc., have been evaluated in different studies to determine their association with acute postoperative pain(Jin et al., 2020; Sng et al., 2018c), but the sample size and number of studies related to the same factor are very limited, and the studies in hysterectomy are rare; whether these factors are associated with acute pain after hysterectomy needs further evaluation in larger cohorts .

Psychological factors that may affect APSP can be mainly divided into three categories: anxiety, depression, and pain catastrophizing. Anxiety is usually identified as a strong risk factor for APSP. Psychological states can either exacerbate or inhibit nociception and the experience of pain through descending modulatory pathways(Tseng et al., 2017). Over 65% of patients experience moderate to severe pain following a hysterectomy. Patients who display challenges in cognitive and emotional assessments have higher levels of acute pain severity (Pinto, McIntyre, Araújo-Soares, et al., 2018). Evidence also showed that preoperative pain catastrophizing, defined as the tendency to focus on and magnify pain sensations and feel helpless in the face of pain, was also associated with APSP, especially between the second and fourth postoperative days (OR =

1.90-2.30)(Wang et al., 2018). Additionally, patients with preoperative pain were more likely to develop acute pain after surgery, which may be related to the increased sensitivity of peripheral pain receptors. Patients using preoperative opioids also had higher postoperative acute pain scores(Menendez et al., 2018). However, reducing the use of opioids before surgery and the rational use of other analgesics can significantly reduce postoperative pain(Manalo et al., 2018).

In a comprehensive study of postoperative pain after various types of surgery, the pain intensity after large joint orthopedics, thoracic surgery, and abdominal hysterectomy is higher compared with other types of surgery(Gerbershagen et al., 2013). Interestingly, the relationship between the length of operation and postoperative pain after hysterectomy remains relatively unexplored. In addition to the long operation times, cancer-related surgeries tend to be more traumatic. Therefore, whether postoperative pain is related to the operation time still needs more relevant research, especially among cancer patients.

Acute pain trajectories

Evaluating trajectories of acute pain resolution could provide novel insights for understanding chronic pain development(Chapman et al., 2011a). The resolution of acute postsurgical pain is a dynamic process. It is affected by the degree of tissue damage, the perioperative pharmacological interaction, and the specific characteristics of the patient. Chronological analysis of the trajectory can provide precise information on the intensity and duration of acute postsurgical pain, as opposed to measuring pain intensity only once, e.g., pain assessment at 1 day after the surgery or mean pain in 2 days after surgery. Recently, group-based trajectory modeling (GBTM) has been established as a statistical method that can be used to determine the number and characteristics of the trajectory clusters for individuals who will have a similar outcome progression over time(M'Bailara et al., 2013). The trajectory modeling approach to the classification of APSP measurement permits

classification of patients into categories such as: 1) resolving pain over time; 2) maintaining a constant level of pain over time; or 3) increasing pain intensity over time(Chapman et al., 2011b, 2012). However, the classification of acute pain trajectories has rarely been studied after hysterectomy(Okamoto et al., 2018).

1.2.1.2 Chronic postsurgical pain (CPSP)

Definition of CPSP

Chronic postsurgical pain has been defined inconsistently in literature(Chapman & Vierck, 2017; Macrae, 2008). A commonly used definition is pain lasting for 2 months after surgery(Katz & Seltzer, 2009). Macrae required 4-point criteria for CPSP(Macrae, 2008): 1) the pain has emerged after surgery, 2) pain persist for at least for 2 months, 3) no other causes for the pain, and 4) the pain after surgery is not a continuation of a preexisting chronic pain condition.

Incidence and consequences of CPSP after hysterectomy

Chronic postsurgical pain (CPSP)usually occurs in about 9%-32% of patients depending on surgical procedure. For example, a multicenter study of CPSP in Europe showed that the 12-month incidence of moderate-to-severe CPSP was 10.8% and the incidence of severe pain was 2.2%(Fletcher et al., 2015). Chronic pain has been well described after procedures such as limb surgery, hernia operation, breast surgery and thoracotomy(Humble et al., 2015; Masselin-Dubois et al., 2013; Thapa & Euasobhon, 2018). Multiple studies since 2000 have evaluated chronic pain after hysterectomy (See Table 1-1). A national questionnaire and database study(n=1299) found that chronic pain was reported by 31.9% one year after hysterectomy(Brandsborg et al., 2007). A two-year multicenter cohort study(n=2929) found that the incidence of chronic pain ranged from 11.8% (vaginal hysterectomy) to 25.1% (abdominal hysterectomy)(Montes et al., 2015). A

prospective observational cohort study(n=870) from China found that the incidence of CPSP at 3 months after hysterectomy was 27.7%(Han et al., 2017). A prospective multicenter cohort study showed that after 3 and 12 months, prevalence of CPSP (numeric rating scale ≥ 4, scale 0–10) was 10.2% and 9.0%, respectively(Theunissen et al., 2016).

Table 1-1 Studies on chronic pain after hysterectomy

Authors and years	Sample size	Study design	Hysterectomy types	Measurement of CPSP (rating scale and range, criterion for CPSP)	Time since surgery when CPSP was collected	CPSP incidence
Benign condition						
(Brandsborg et al., 2007)	1299 women	Nationwide questionnaire and database study	Total abdominal/Subtotal abdominal/Vaginal/ Laparoscopically assisted vaginal/Laparoscopic hysterectomy	Yes/No for pelvic pain experienced in the past 3 months within a pain response questionnaire	12 months	31.9% for chronic pain before surgery and 14.9% women did not have preexisting pain before surgery
(Pinto et al., 2012)	186 women	A prospective study	Abdominal laparoscopic, vaginal, and vaginal assisted laparoscopic/Open abdominal hysterectomy	Numeric rating scale range from 0-10, >0 identified as having CPSP	4 months	50%
(Pinto, McIntyre, Araújo-Soares, et al., 2018)	203 women	A prospective study	Abdominal laparoscopic, vaginal, and vaginal assisted laparoscopic/Open abdominal hysterectomy	Yes/No for surgery-related pain within a telephone call	5 years	17.1%
(Montes et al., 2015)	766 women	A prospective study	Vaginal/Abdominal hysterectomy	Numeric rating scale range from 0-10, >0 identified as having CPSP	4 months	11.8% for vaginal hysterectomy and 25.1% for abdominal hysterectomy

					14 months	4.1% for vaginal hysterectomy and 9.9% for abdominal hysterectomy
					26 months	2.2% for vaginal hysterectomy and 6.7% for abdominal hysterectomy
(Pokkinen et al., 2015)	242 women	A prospective study	Vaginal/laparoscopic hysterectomy	Numeric rating scale range from 0-10, >0 identified as having CPSP	6 months	26.0%
(Theunissen et al., 2016)	468 women	A prospective study	Total or subtotal hysterectomy	Numeric rating scale, range from 0 – 10, ⩾ 4 identified as having CPSP	3 months	10.2%
					12 months	9.0%
(Beyaz, Özocak, et al., 2016)	93 women	A prospective study	Total abdominal hysterectomy	Numeric rating scale range from 0-10, >0 identified as having CPSP	More than 3 months	30.1%
(Han et al., 2017)	870 women	A prospective study	Lower abdominal/Pfannenstiel/Vaginal/ Laparoscopic/ Vaginal assisted laparoscopic	Numeric rating scale range from 0-10, >0 identified as having CPSP	3 months	27.7%
	216 women				4 months	32%

(Sng et al., 2018c)		A prospective study	Abdominal/Laparoscopic hysterectomy	Yes/No for surgery-related pain within a telephone call	6 months	15.7%
(Jin et al., 2020)	406 women	A prospective study	Abdominal/Laparoscopic hysterectomy	Numeric rating scale range from 0-10, >0 identified as having CPSP	3 months	20.9% for laparoscopic hysterectomy and 20.4% for abdominal hysterectomy
					6 months	11.6% for laparoscopic hysterectomy and 9.4% for abdominal hysterectomy
					12 months	5.8% for laparoscopic hysterectomy and 6.1% for abdominal hysterectomy
(As-Sanie et al., 2019)	176 women	A prospective study	Open/Laparoscopic or Robotic/Vaginal hysterectomy	Numeric rating scale ranging from 0-10, less than 50% improvement in pelvic pain severity before hysterectomy defined as CPSP	6 months	11.9% of women with presurgical chronic pain reported persistent pelvic pain
(Hoofwijk et al., 2019)	345 women	A prospective study	Total laparoscopic/Vaginal-or laparoscopic-assisted vaginal/abdominal hysterectomy	Numeric rating scale, range from 0 – 10, ⩾ 4 identified as having moderate to severe CPSP	3 months	10.5%
					12 months	7.9%
(Tan et al., 2020)	216 women	A prospective study	Abdominal/Laparoscopic hysterectomy	Numeric rating scale, range from 0 – 10, ⩾ 3	4 months	23.2%

				identified as having CPSP	6 months	11.1%
(Grundström et al., 2022)	16694 women	A retrospective study	Abdominal/Vaginal /Laparoscopic hysterectomy	YES/No from the 1-year patient questionnaire ("Do you have pelvic pain/lower abdominal pain? yes/no")	12 months	22.4%
Cancer						
(Sørensen et al., 2015)	177 women with gynecological cancer	An observational study	Abdominal and Robot-Assisted Laparoscopic Hysterectomy	Numeric rating scale > 0, scale 0 – 10	Average 36 months for abdominal hysterectomy and 31 months for laparoscopic hysterectomy	16.9% for abdominal hysterectomy and 11.9% for robot-assisted laparoscopic hysterectomy
(Lunde et al., 2019)	207 women with endometrial cancer	A cross sectional follow up study	Robot-assisted hysterectomy	Numeric rating scale range from 0-10, >0 identified as having CPSP	More than 24 months	14.9%
(Saxena et al., 2016)	21 women with ovarian cancer	A cross sectional follow up study	Staging laparotomy for carcinoma ovary	Numeric rating scale, range from 0 – 10, ⩾ 4 identified as having moderate to severe CPSP	1 month	90.5%
					2 months	38.1%
					3 months	38.1%

CPSP significantly increases the incidence of emotional distress, insomnia, and other health problems, which not only brings suffering to patients, but also creates millions of dollars in excess medical expenditures and an associated social burden(Nadeau et al., 2021). According to epidemiological surveys, more than 100 million adults in the United States alone suffer from chronic pain each year, and the annual direct (treatment costs) and indirect (productivity loss) economic losses due to pain are as high as $650 billion, far more than any other economic losses due to disease(Gaskin & Richard, 2012). Since a proportion of patients develop chronic pain after hysterectomy, it is imperative to identify high-risk individuals to effectively prevent the occurrence of severe postoperative acute and chronic pain.

Gynecological cancer is a major health burden globally. Approximately 94,000 people are diagnosed with a gynecologic cancer each year(Centers for Disease Control and Prevention, 2019). Abdominal hysterectomy is a common way to treat gynecological cancer. However, based on studies identified in Table 1, CPSP has rarely been studied in the context of gynecologic cancer. One recent study among 21 ovarian cancer patients found the incidence for moderate to severe CPSP (Numeric rating scale ≥ 4) 3 months after surgery was 38.1%(Saxena et al., 2016), which is much higher than for patients having hysterectomy for benign indications. Another study of 177 gynecological cancer patients found the incidence for CPSP (NRS >0) for abdominal hysterectomy was 16.9%(Sørensen et al., 2015).

Risk factors for CPSP

CPSP has been identified as an important postoperative complication. Therefore, it is particularly important to identify the factors that predict the occurrence of chronic pain at an early

stage to create interventions to prevent the occurrence of chronic pain. Chronic pain-related risk factors have many similarities to acute pain-related risk factors but also have their own unique associated risk factors.

In terms of sociodemographic/lifestyle factors, young, female, high BMI, preoperative patients who smoke (or have quit smoking) are more likely to develop chronic pain. Also, psychological factors such as pain catastrophizing, anxiety and depression are all related to the occurrence of postoperative chronic pain. A recent meta-analysis stated that psychological predictors have a significant association with chronic postsurgical pain (CPSP) and that state anxiety is the most explicative one(Giusti et al., 2021). A recent review from Emanuele (2021) also showed state anxiety, trait anxiety, depression, catastrophizing all has independent significant associations with chronic postsurgical pain(Giusti et al., 2021). In addition to demographic and psychological factors, evidence showed that patients with preoperative chronic pelvic pain were more likely to develop chronic pain after hysterectomy(As-Sanie et al., 2021).

CPSP is also related to surgical procedures. Hysterectomy is done using a variety of surgical methods, including abdominal, laparoscopic, vaginal, total or subtotal hysterectomy. The effect of surgical modality on chronic pain is currently debated. One study found that the incidence of chronic pain 4 months after surgery was 25.1% for abdominal hysterectomy and 11.8% for vaginal hysterectomy (Montes et al., 2015). In another prospective study, Pinto and colleagues further indicated that abdominal hysterectomy (median incision and Pfannenstiel incision) was a predictor of chronic pain(Pinto et al., 2012). However, a study by Brandsborg et al. did not find differences in the incidence of CPSP after different types of hysterectomy, and therefore believed that the effect of surgery itself on chronic pain was small(Brandsborg & Nikolajsen, 2018a). Another cross-sectional study found no difference in the incidence of chronic pain between robotic-assisted

laparoscopic hysterectomy and abdominal hysterectomy, which seems to support Brandsborg's conclusion(Sørensen et al., 2015). However, most studies are in begin patient populations. To conclude, the effect of surgical methods on CPSP after hysterectomy remains to be confirmed by multicenter, large-sample studies among patients with cancer.

Importantly, although some studies have investigated the incidence and risk factors of CPSP following hysterectomy for benign indications, little is known about the characteristics that put patients with gynecological cancer at risk for CPSP after hysterectomy. The extent of surgery (time in surgery, sub-total vs total hysterectomy, surgical staging procedures) and adjuvant chemotherapy and radiation therapy are likely to have a major influence on postoperative pain. In addition, the psychological stress of surgery and diagnosis is likely to be worse in patients with gynecological cancer compared to benign tumors and could also impact development of CPSP. Therefore, there is a need for large sample studies to explore incidence and risk factors for CPSP in patients with gynecological cancer.

1.2.1.3 The relationship between APSP and CPSP

Many studies have suggested that APSP is closely related to CPSP. The intensity of APSP has been shown to be a major risk factor for several CPSP(Nikolajsen & Minella, 2009; Theunissen et al., 2016), but studies evaluating the influence of APSP on CPSP usually use average pain intensity within 24 to 1 week after surgery. For example, a cohort study of patients with breast cancer found that the 6-day NRS score at rest after surgery was significantly associated with CPSP 3 months after surgery(Hashimoto et al., 2018). VanDenKerkhof's cohort study found women with pain intensity >3/10 NRS during the post-op period and >3/10 NRS at discharge had a higher risk of developing CPSP after gynecological surgery. Instead of capturing APSP intensity at single time

or using mean pain scores, evaluations of APSP pain trajectories would be a novel approach and potentially important approach to advance understanding of the relationship between APSP and CPSP. Acute pain trajectory analyses capture information about both pain intensity and pain evolution over multiple post-operative days, which will help to predict CPSP more precisely. For example, a previous study among patients with breast cancer clustered APSP into 3 trajectory models: moderate to mild, moderate to moderate, severe to severe, and the study found only severe to severe pain cluster was significantly associated with CPSP at 6 months(Okamoto et al., 2018). The ROC-AUC analysis of the study confirmed that there was a better precision for CPSP by acute pain trajectories compared to pain intensity one day after surgery. A cohort study of patients seen in an emergency department identified patients with different acute pain evolution trajectories and found that patients with moderate to severe pain trajectories and those with severe-to-severe pain trajectory were more likely to develop chronic pain compared to patients in the low final pain trajectories(Okamoto et al., 2018). To date, the relationship between acute pain trajectories and development of CPSP has not been studied in patients following hysterectomy for a gynecological cancer.

1.2.2 Significance

The proposed study is timely and significant because it will address knowledge gaps in understanding about the development of CPSP after hysterectomy for patients with gynecologic cancer. Clinically, the study results have potential to guide early identification of gynecological cancer survivors most vulnerable to developing CPSP. Findings from this study will also provide

the basis for a future program of research to provide targeted, tailored, and more effective pain management based on risk for CPSP after surgery for gynecologic cancers.

1.2.3 Innovation

The proposed study innovates by leveraging detailed acute pain trajectory data following hysterectomy in patients with gynecologic cancer to shed light on CPSP development. This marks a departure from traditional research methodologies that often rely on average pain scores or single time-point assessments to explore APSP and CPSP connections. By focusing on the evolution of pain post-surgery, our research will provide a nuanced understanding of pain dynamics and identify potential trajectory-specific risk factors, offering fresh perspectives on the risk elements of APSP and CPSP. By investigating how initial pain trajectories relate to subsequent healthcare utilization, specifically 30-day readmission rates, and prolonged opioid use, this aim addresses a critical gap in the continuum of support for gynecologic cancer patients' postsurgical experiences. This forward-looking approach not only underscores the predictive value of early pain experiences but also illuminates how they may influence healthcare resources and patient wellbeing long after the surgical.

Moreover, there is a notable research gap regarding CPSP in the context of gynecologic cancer. Typically, patients with cancer undergo longer and more invasive surgeries and may receive adjunct therapies like chemotherapy or radiotherapy, factors not thoroughly examined in current CPSP literature. This research will comprehensively evaluate such variables, potentially uncovering key insights into CPSP risks for cancer patients and guiding the creation of targeted preventative strategies.

1.3 PRELIMINARY STUDIES

1.3.1 State of the science

The first major step in establishing the state of the science in post-operative pain for patients with gynecological cancer included a review to synthesize the research between January 2010 to January 2022 on the operationalization of APSP and CPSP and risk factors for each among patients with cancer. Four databases were searched for papers published in English, which included: PubMed, Cochrane Library, Web of Science and Embase. There were 20 studies that evaluated acute and chronic pain postoperatively for patients with cancer from 2010 to 2022; 11 were RCTs, and 9 of them were prospective longitudinal studies. Among the 20 studies, 16 studies focused on women with breast cancer; the investigation about APSP and CPSP in gynecological cancer is rare. Although similar tools for pain measurement were used such as numerical rating scale (NRS) or visual analog scale (VAS), researchers used different cut off values for clinically significant chronic pain across studies. For example, in Habib's study, the definition of chronic pain is NRS>=3 or any item of BPI>0(Habib et al., 2019b). In Honerlaw's study, the BPI pain intensity >=5 is categorized as CPSP. In Fujii's study, the definition of CPSP is NRS>=1. Under the different cut-off values, CPSP incidence varies widely from 8% to 75%(Fujii et al., 2019). The most frequently assessed aspect of clinical pain is sensory intensity, which was included in all identified papers. Pain interference (how unpleasant or disturbing the pain feels) was also commonly used. Anxiety, depression, surgical worry, and pain catastrophizing have been identified as important potential predictors of CPSP(Bruce et al., 2014) . Additionally, in a study investigating post-surgical anxiety, we found the change in anxiety post surgically is associated

with CPSP(Kyranou et al., 2013). Previous reviews stated that psychological factors would influence the risk for APSP, but for CPSP, there are some controversary(Giusti et al., 2021). For example, in our review, in VanDenKerkhof's study trait anxiety is not associated with CPSP(Bruce et al., 2014; VanDenKerkhof et al., 2012). However, in Bruce's study, he found trait anxiety is closely related with CPSP.

The findings from this preliminary study advances understanding about the measurement of acute and chronic post-surgical pain for patients with cancer. Implications suggest there is a need to measure multiple domains of chronic pain and develop multidisciplinary cooperation strategies to manage and prevent chronic pain specially for cancer patients. The review directly helped us to operationalize CPSP in the proposed study.

1.3.2 A time-varying effect analysis about pain and emotions during chemotherapy for patients with gynecologic cancer

Pain is a common distressing symptom for women with gynecologic cancer. Although there is evidence of associations between pain and emotions such as anxiety and depression, the pattern of relationships over time during chemotherapy has not been studied. This secondary analysis study aimed to 1) evaluate the dynamic associations between emotions (anxiety, depression) and pain during chemotherapy for individuals with gynecologic cancer, and 2) explore baseline personality characteristics (neuroticism and conscientiousness) as potential moderators of the association between emotions and pain. Twenty-seven participants who completed at least 4 cycles of paper-and-pencil daily diary monitoring for pain, anxiety, and depression during chemotherapy were included in the analysis. Participants rated daily symptom severity (0-10) at their worst in the past

24 hours. Time-varying effect models (TVEM) showed significant, yet decreasing, effects of anxiety over time (coefficient range: 0.66-0.23) and depression (coefficient range: 1.21-0.43) on pain during the 4 cycles. Multilevel modeling supported significant associations between pain and anxiety ($b=0.24$, $SE=0.06$, $p<0.01$) and depression ($b=0.30$, $SE=0.08$, $p<0.01$). Neuroticism moderated the association between anxiety and pain ($b=0.15$, $SE=0.06$, $p<0.05$); whereby anxiety was more strongly associated with pain in those with higher neuroticism.

This study found significant temporal relationships between emotions and pain in individuals with gynecologic cancer during chemotherapy. Findings also suggest that neuroticism moderates the relationship between mood and pain. The findings can inform future pain prevention research and lay a foundation for tailored psychosocial symptom management interventions during chemotherapy

1.3.3 Relevance and transition to the proposed dissertation study

The review of the measurement of APSP and CPSP revealed that CPSP among patients with gynecologic cancer is understudied with most studies focusing on breast cancer. Among the identified studies that explored relationships between APSP and CPSP, we found studies evaluating the influence of APSP on CPSP usually used average pain intensity within 48 or 72 hours after surgery. The rates at which acute pain resolves after oncology surgery and how acute pain resolution would influence CPSP is still unclear. The proposed dissertation study aims to fill these research gaps to evaluate the association between acute pain trajectories and CPSP to comprehensively present the effect of both acute pain resolution and pain intensity. Also, this review helped use to understand how CPSP and APSP have been operationalized among studies. The proposed dissertation study would operationalize CPSP and APSP based on these previous studies.

The quantitative analysis was not only a method preparation for the proposed dissertation, which will include time varying effects, but also advanced our understanding about the relationship between pain and emotions over time in patients receiving chemotherapy for gynecologic cancer. Anxiety and depression were both significantly associated with pain experience, while the magnitude of the association decreased over time. The proposed dissertation will use anxiety and depression diagnosis as the risk factor for the relationship between acute pain trajectories and CPSP. The multilevel modeling method we used in this quantitative analysis will be used for the proposed dissertation study Aim 3 (Explore whether patient-related factors and medical

characteristics moderate the relationship between acute pain trajectories and chronic pain). The results have potential to inform pain management strategies for patients with gynecologic cancer.

1.4 RESEARCH DESIGN AND METHODS

1.4.1 Design and approach

Enhanced Recovery After Surgery (ERAS) is now firmly established as a global surgical quality improvement effort to reduce perioperative complications and accelerate recovery (Kehlet & Joshi, 2017). This ancillary study of an existing large dataset of patients enrolled in an ERAS protocol will allow us to answer the following aims in a sample of adult (>18) patients with gynecologic cancer who underwent abdominal hysterectomy. We will extract data from the ERAS dataset to understand postsurgical pain among patients with gynecological cancer after abdominal hysterectomy (including total abdominal hysterectomy, robotic assisted abdominal hysterectomy, and laparoscopic abdominal hysterectomy). All patients who meet our inclusion criteria in the dataset from January 1st ,2019 to December 31st, 2021, will be included in the analysis.

Aim 1: Determine distinct post-operative acute pain trajectories over 5 days following hysterectomy for a gynecological cancer, and evaluate factors associated with trajectory membership.

- Aim 1.1 The study proposes to use group-based trajectory models to generate acute pain trajectories. The fit estimates both pain intensity and rate of pain resolution, thus

increasing the information that pain assessment provides and giving us a more comprehensive understanding of different trajectories of APSP.

- Aim 1.2 To identify determinants of acute pain trajectories, multinomial regression models will be constructed to determine associations between baseline factors (demographic factors, medical factors, and surgery related factors) and trajectories of acute pain with adjustment for potential confounders.

Aim 2: Examine the relationships between acute pain trajectories and the development of chronic pain.

- Predictive value of the acute pain trajectory for the presence of pain at 1 and 2 months after surgery will be assessed using logistic regression analyses for each timepoint.

Exploratory Aim3: Explore whether patient-related factors and medical characteristics moderate the relationship between acute pain trajectories and chronic pain.

- A multivariate regression approach will be conducted to examine whether risk factors for CPSP (age, surgical methods, and perioperative opioid use) moderate the relationship between acute pain trajectories and CPSP at 1 month and 2 months.

1.4.2 Setting and Sample

1.4.2.1 Setting and Sample

Data will be extracted from the University of Pittsburgh Medical Center (UPMC) ERAS dataset and medical records for patients undergoing abdominal surgery from January 1st ,2019 to December 31st, 2021.

1.4.2.2 Inclusion criteria

The ERAS dataset (2019.01.01 – 2021.12.31) will serve as our sampling frame. Adult woman (> 18 years of age) with suspected gynecologic cancer (e.g., ovarian, fallopian tube, or primary peritoneal cancer) operated on by gynecologic oncology surgeons through abdominal hysterectomy will be included. Screening of the ERAS dataset identified 2354 patients who had abdominal hysterectomies by gynecologic oncology surgeons. Of those, 1342 patients had a confirmed gynecologic cancer diagnosis and are eligible for inclusion in this study.

With a sample of n=1342 and 30 predictors, we will have >0.99 power to fit and test the multivariate regression model for aim 1 at a significance level of 0.05 and medium effect size (f^2) of 0.15.

1.4.2.3 Exclusion criteria

Patients without any medical records about clinical visits after surgery will be discussed and confirmed by our research team and be excluded from the study.

1.4.3 Data collection procedures

All the data will be collected and combined in Qualtrics, an online survey system to create survey, collect and store data. First, we would upload ERAS dataset in Qualtrics, and screen patients by our inclusion and exclusion criteria through medical records. After excluding patients with benign findings on surgical pathology, we then will collect data from medical records and combine information with ERAS dataset. The combined dataset will be stored in Qualtrics and

only study investigators have access to the data. The details of data collected from medical records and ERAS dataset are described below in Table 1-2.

1.4.4 Measures

Data extracted from the ERAS dataset and medical records are described in Table 1-2. The practice manual of data collection from medical records is in in Appendix C.

Table 1-2 Operationalization of variables in the proposed study

Variables	Source	Operationalization
Baseline factors- Sociodemographic/lifestyle factors		
Age	ERAS dataset	Age at surgery from ERAS dataset
Marital status	Medical records	1–Married; 2 – Widowed; 3 – Separated; 4 – Divorced; 5 - Single
Smoking	Medical records	1 – Never smoker; 2 – Former smoker; 3 – Current smoker; 4 – Unknown
Alcohol	Medical records	1-Yes; 0-No
BMI	ERAS dataset	BMI at surgery from ERAS dataset
Employment status	Medical records	1 – Unemployment; 2 – Full time; 3 – Part time; 4 – temporary employee
Zip code	ERAS dataset	5-digit zip code
Baseline factors- Medical history		
Diagnosis	Medical records (surgical pathology report)	Categorize cancer diagnosis into: 1-Endometrial cancer; 2-Ovarian Cancer; 3-Cervical Cancer; 4-Fallopian Tubal Cancer; 5-Peritoneal Cancer
Cancer stage	Medical records (Surgical pathology report)	Use FIGO stage
Comorbidities	ERAS dataset and medical records	1-Yes; 0-No for the following comorbidities: coronary artery disease (CAD), myocardial infarction (MI),

		congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), hyperlipidemia, acute chronic renal failure, pneumonia, hypertension, diabetes, severe mental illness and atrial fibrillation and any other comorbidities mentioned in medical records post-operatively.
Previous abdominal surgery	Medical records	Step 1: 1-Yes; 0-No for previous abdominal surgery Step 2: record the type of previous abdominal surgery if YES Step 3: record the date of previous abdominal surgery if YES Step 4: calculate the interval days of previous abdominal surgery and the specific cancer treatment surgery
Neoadjuvant chemotherapy	Medical records	1-Yes; 0-No
Anxiety diagnosis	Medical records	1-Yes; 0-No from Epic problem list
Depression diagnosis	Medical records	Step 1: 1-Yes; 0-No from Epic problem list
Baseline factors- Surgical-related factors		
Operation date	ERAS dataset	Record date
Presurgical opioid use	Medical records	1-Yes; 0-No
Presurgical pelvic pain	Medical records	Step 1:1-Yes; 0-No from Epic Step 2: if yes, record the pain intensity and descriptions about presurgical chronic pain
Surgery procedure	ERAS dataset	1-Hysterectomy total abdominal BSO; 2-Hysterectomy total abdominal; 3-Abdominal hysterectomy robotic assisted; 4-Abdominal hysterectomy laparoscopic; 5-Abdominal hysterectomy BSO robotic assisted; 6-Abdominal hysterectomy BSO laparoscopic
American Society of Anesthesiologists Classification (ASA class)	ERAS dataset	ASA I -A normal healthy patient; ASA II-A patient with mild systemic disease without significant functional limitation; ASA III-A patient with severe systemic disease with significant functional limitation; ASA IV-A patient with severe systemic disease with constant threat to life

Surgery procedure time (in minutes)	ERAS dataset	Mean (SD)
Postsurgical outcomes		
Acute pain	ERAS dataset	Daily mean pain severity (0-10) over 5 postsurgical days
Chronic pain intensity	Medical records	Routine pain assessment at clinical visits (0-10) plus clinical notes at 2 weeks, 1 month, 2 months and 3 months after surgery
Chronic pain location	Medical records	Clinical notes at 2 weeks, 1 month, 2 months and 3 months after surgery
Opioid use one week after surgery	ERAS dataset	1-Yes; 0-No
Opioid use	Medical records	1-Yes; 0-No at 2 weeks, 1 month, 2 months and 3 months after surgery
Post-surgical length of stay at hospital (in days)	ERAS dataset	Mean (SD)
Readmission within 30 days after surgery	ERAS dataset	1-Yes; 0-No (If yes, record the interval days of readmission)

1.4.5 Data analysis plan

1.4.5.1 Descriptive statistics

Data will be analyzed using IBM SPSS Statistics (Version 27) for descriptive and exploratory data analyses. Unless otherwise specified, the level of statistical significance will be set at 0.05. A detailed descriptive analysis of all variables will be performed to describe data. Describe univariate sample distribution of the single variables between and within subjects including their central tendency and dispersion based on the level of measurement. Dependent variables in this study are pain intensity at different visits which is reflected by NRS scores.

1.4.5.2 Data screening procedures

A detailed exploratory analysis of all data will be performed to identify any data anomalies (e.g., outliers, missing data). The results of exploratory analyses will be used to assess outliers, analyze missing data, and check underlying assumptions of planned analyses.

Outlier assessment:

We will plot demographic variables such as age and BMI using boxplots to find outliers. If there are any outliers, we will look back to the original data to see if it is a coding error, a random outlier, or underlying a potentially interesting psychological process. Within every individual, trajectories of daily pain and opioid use after surgery will be depicted to see the trend of change and if there are any outlier trajectories. Bivariate sample distribution will also be described between pairs of variables including contingency tables, graphical representation and quantitative measures of dependence. Through the process, we will determine whether there are any bivariate outliers. This step is not simply descriptive analysis, it can also help to identify associations between/among variables to see if there is need for adjustment of confounders or covariance. We will use SPSS 26.0 to identify any multivariate outliers using multiple linear regression for independent variables. Linear regression can generate a new variable corresponding to the Mahalanobis Distances for the combination of independent variables. Then we compare these Mahalanobis Distances to a chi-square distribution with the same degrees of freedom. By using the formula (1 – CDF.CHISQ (Mahalanobis Distances variable, df)), we will calculate the p-value of the right-tail of the chi-square distribution. Multivariate outliers will be present wherever the values of the new probability variable are less than .001. Prior to running inferential analyses, it is advisable to remove these cases(Black et al., 2011).

Missing data:

The randomness of missing data between patients and within patients will be investigated to assess the amount and patterns of missing data. For intensive longitudinal data, one common problem is the presence of missing data especially for pain assessment. Pain is particularly prone to nonignorable missingness, namely, missingness where the missing data mechanism depends on unobserved information. For example, it is possible that the participants may opt not to report their feelings on the days with heightened pain level, thereby leading to nonignorable missingness when modeling emotion processes. However, in our case, the post-surgical acute pain information is collected by clinicians, the missing data is at random assumption. Mixed model repeated measures could handle missing data in the outcome with the help of 2 week and 2-month pain assessments when 1 month or 3-month assessments are missing. Missing data is ignorable when a variable can be accounted for or explained by other variables. These nonresponse relevant variables may be covariates of the variable with missing data, or early observed measures of the variable itself. However, if the data are missing not at random when the missingness is a function of the unobserved values themselves, even after controlling for other variables, the condition is often non-ignorable (Black et al., 2011). Strategies used to handle missing data like multiple imputation, Bayesian estimation, case deletion will be considered.

Checking assumptions:

We will check for violations of statistical assumptions including normality of the distribution and residuals of the model we intend to use, linearity, and homogeneity of variance. To be specific, we will plot the residuals of each regression model. If the plot is random, the linearity assumption hasn't been violated. Then we will use Levene's Test to check the homogeneity of variance. When $p>0.05$, we can say that the variance of the residuals is equal and therefore the assumption of

homoscedasticity is met(Barbara G. Tabachnick & Linda S. Fidel, 2007). To check if the residual of the model is normally distributed, we will use Q-Q plots to present residuals of regression models. If assumptions are violated, data transformation or more robust statistical methods will be used. Highly skewed data are often transformed by taking square root because our daily assessment pain variable contains a high frequency of 0 values.

1.4.5.3 Data analysis procedures

For aim1.1, to characterize trajectories of acute pain, a group-based trajectory modeling approach will be used to depict distinct patterns of acute pain following surgery. Group-based trajectory modeling is a statistical approach that identifies groups of patients with similar evolution over time—in this study, pain intensity resolution during a 5-day period—without assuming the existence of a specific trend or number of groups(Nagin & Odgers, 2010). This method requires at least 100 participants (ideally more than 300) and a minimum of 3 time points. It quantifies both initial pain intensity and rate of pain resolution. The first group-based trajectory modeling step is usually to determine the number of trajectories that best fit the data. Bayesian information criteria will be used to determine the best model(Nagin & Odgers, 2010). The second group-based trajectory modeling step is to characterize the shapes of each trajectory by fitting it to a linear, quadratic, or cubic polynomial pain evolution pattern.

For aim 1.2, to identify determinants of acute pain trajectories, multinomial regression models will be constructed to determine associations between baseline factors (demographic factors, medical factors, and surgery related factors) and trajectories of acute pain with adjustment for potential confounders. Risk factors including age, surgical methods, length of surgery and perioperative opioid use will be examined to see if they are associated with acute pain trajectory

groups. The covariates are medical histories (cancer stage, BMI, preoperative chronic pelvic pain, history of abdominal surgery, history of cesarean section, history of smoking), mental disorder diagnosis and baseline pain (preoperative pain intensity). Each potential predictor will be assessed to determine whether it would result in a better fitting model. Predictors with a p value of <0.25, which indicates a lack of significant effect, will be excluded from further model testing. All potential significant predictors from the analysis will be entered into the model to predict each individual change parameter. Only predictors that maintain a statistically significant contribution in conjunction with other variables will be retained in the final model. A p-value of < .05 indicates statistical significance.

For aim 2, the predictive value of acute pain trajectory membership on the presence of pain at 1- and 2-months post-surgery will be evaluated using separate logistic regression analysis for each timepoint. Age, BMI, diagnostic, surgical procedure, ASA class, presence of an anxiety diagnosis, receipt of neoadjuvant chemotherapy, preoperative opioid use, and preoperative pelvic pain will be used as covariates. The study will screen potential covariates one at a time using t test for continuous variables (or Kruskal-Wallis H test if homogeneity of variances was violated), and Chi-square test (or Fisher exact test if sparse cells are encountered) for categorical variables. Variables that are not significant at the 0.25 level in the univariate analysis will not be included in the multivariate multinomial logistic regression (Barbara G. Tabachnick & Linda S. Fidel, 2007). A backward stepwise approach will be used to create a parsimonious model. Statistical tests will be 2-sided, and only predictors with $p < 0.05$ will be retained in the final model. Area under the curve (AUC) of the ROC curve will be calculated to determine predictive accuracy of acute pain trajectories.

For aim 3, to explore whether patient-related factors and medical characteristics moderate the relationship between acute pain trajectories and chronic pain, generalized linear models (GLMs) will be utilized. The primary independent variable will be acute pain trajectory group membership. Potential covariates such as age, BMI, diagnostic category, surgical procedure, ASA class, presence of an anxiety diagnosis, receipt of neoadjuvant chemotherapy, preoperative opioid use, and preoperative pelvic pain will be controlled for in the models. These covariates will be selected based on clinical relevance and potential to moderate the relationship between APSP and outcomes (Chapman et al., 2011b, 2011a, 2012; Imai et al., 2021). Prior to GLMs, univariate analyses will be conducted to identify variables significantly associated with the outcomes. Continuous variables will be assessed using t-tests or Wilcoxon rank-sum tests if non-normality is present. Categorical variables will be assessed using Chi-square or Fisher's exact tests as appropriate. Variables with a p-value less than 0.25 in univariate analyses will be considered for inclusion in the multivariable models. Odds ratios with 95% confidence intervals will be computed to estimate the relative risk of the outcomes associated with each acute pain trajectory, adjusted for other covariates in the model.

1.5 STUDY TIMELINE

Table 1-3 Study Timeline

Study activities	2022.07-2022.09	2022.10-2022.11	2022.11-2023.01	2023.02-2023.06	2023.07-2023.08
Data collection	**X**	**X**			
Data cleaning		**X**			

Data analysis		**X**	**X**	**X**	
Abstract and manuscript dissemination			**X**	**X**	**X**
Dissertation defense					**X**

1.6 POTENTIAL LIMITATIONS AND ALTERNATIVE APPROACHES

One limitation of the proposed study is that the assessment of Chronic Post-Surgical Pain (CPSP) will rely on data extracted at 1- and 2-months post-surgery from medical records. To enhance the robustness of our CPSP evaluation, we will meticulously gather information on pain characteristics, including location, intensity, and descriptions as recorded in medical documentation. Additionally, to mitigate potential gaps in chronic pain data at the 1 and 2-month marks, pain assessments documented during postoperative visits at 2 weeks and 3 months will be utilized to impute any missing information. It is recognized that the timing of post-surgery visits may not align precisely with the 1 and 3-month intervals; hence, data from visits that most closely coincide with these intervals will be prioritized for analysis. Should the pain trajectories anticipated by the study not materialize among patients with gynecological cancer after hysterectomy, the research methodology includes contingency strategies to investigate and analyze the available pain data comprehensively. This may involve examining alternative patterns in the pain trajectory data and exploring their clinical significance, even if they differ from expected outcomes.

The study also collected prolonged opioid use and 30-day readmission. Thus, in the absence of significant CPSP findings, the study remains poised to deliver substantial clinical insights into the prolonged opioid use and readmissions following hysterectomy in women with gynecological cancer. Such insights could inform improvements in postoperative care and highlight potential areas for further investigation in minimizing adverse outcomes after surgery.

1.7 PROTECTION OF HUMAN SUBJECTS AND REDUCTION OF RISKS

As this study has no direct contact with participants, there is no direct risk associated with this proposed study. This study was conducted with the approval of the University of Pittsburgh's Office of Human Subjects Research Protection (STUDY20050087). Breach of confidentiality is a potential risk in any research study. Information linking the participant's identity with her ID in the ERAS dataset is maintained by the study investigator in a password-protected computer file. The investigators will follow the guidance from the U.S Department of Health & Human Services [HHS15] and work with the IRB officer to ensure the data is not identifiable. De-identified data for this ancillary analysis will be maintained by this investigator on a password-protected computer.

2.0 SUMMARY OF STUDY

2.1 CHANGES TO PROPOSED STUDY

Reviewed here are the changes to the originally proposed study related to data collection and analysis procedures. This section is intended as a bridge between the proposed study and the dissertation study.

2.1.1 Data collection

Area Deprivation Index (ADI): Unfortunately, the vast majority of zip codes recorded in ERAS and medical records were 5 digits instead of 9, which precluded the identification of the Area Deprivation Index (ADI) for our study.

Data Management: Originally, we planned to collect and amalgamate all data within Qualtrics, an online system for creating surveys, as well as for collecting and storing data. However, given the large sample size of 1,343 patients, to expedite data collection, we divided the medical review data into two segments: baseline factors (collected by Margaret Flanigan and Gabriella Ficerai-Garland) and post-surgical outcomes (collected by Sarah G Bell and Jian Zhao). All data were gathered in de-identified Excel files and were subsequently combined by Jian Zhao.

2.1.2 Samples for Aim 2 and Aim 3

In our original plan, we proposed to explore the relationship between acute pain trajectories and the development of chronic pain. However, upon completion of data collection, we discovered that over 60% of our dataset consisted of patients with low-grade, early-stage endometrial cancer, who typically have a singular post-operative follow-up for postsurgical follow up visit or staple removal, limiting our ability to track CPSP at 2-months post hysterectomy. In contrast, patients with high-risk endometrial and ovarian (including fallopian and primary peritoneal) cancers, who undergo adjuvant or neo-adjuvant chemotherapy, provide a wealth of data through monthly follow-ups, allowing for a thorough examination of their pain and opioid use through the first 2-months post hysterectomy. Thus, we've adjusted our sample for Aim 2 and Aim 3 to focus on this high-risk gynecological cancer population, which would allow for more detailed and consistent data regarding CPSP due to their more frequent follow-up schedule. This shift in focus could potentially provide more reliable insights into the treatment and management of CPSP in a more vulnerable subset of the gynecological cancer population.

2.1.3 Outcomes for Aim 2 and Aim 3

In the original plan, our focus was solely on chronic postsurgical pain as the primary outcome. Nonetheless, during the data collection phase, we concurrently gathered information on 30-day readmission and prolonged opioid use at 1 week, 2 weeks, and 2 months post-hysterectomy. APSP is not merely a determinant of prolonged hospitalization and increased healthcare costs; it also has a demonstrated association with significant postoperative complications, including cardiovascular

and thromboembolic events (Gan, 2017). However, the study about the impact of APSP trajectories is rare. Hence, the additional data on readmission and opioid use could greatly enrich our understanding of the implications of APSP trajectories. Consequently, the dissertation study has been expanded to not only examine the association between APSP trajectories and CPSP but also to explore how APSP trajectories are related to 30-day readmission and prolonged opioid use after abdominal hysterectomy in patients with high-risk gynecological cancer.

Based on the above changes about samples and outcomes in Aim 2, now we have:

Aim 2: Examine the relationships between acute pain trajectories and the development of chronic pain, 30-day readmission and prolonged opioid use after abdominal hysterectomy in patients with high-risk gynecological cancer.

- Aim 2.1 Evaluate the bivariate correlations between acute pain trajectories and the development of chronic pain, 30-day readmission and prolonged opioid use.
- Aim 2.2 Using multivariate regression analysis to delineate the relationships between acute pain trajectories and the development of chronic pain, 30-day readmission and prolonged opioid use adjusting for the covariates including demographic, medical and perioperative factors.

2.1.4 Persistent postsurgical pain

Our original research plan was to collect post-surgical pain data at approximately 2 weeks, 1 month, 2 months, and 3 months following a hysterectomy, with CPSP at 1 month and 2 months serving as the dependent variables for analysis in Aim 2 and Aim 3. However, during the actual data collection process, we observed that the majority of patients had their first follow-up visit at

around 2-3 weeks after surgery. We seldom encountered high-risk gynecological cancer patients who returned exactly at one month; it was more common for low-grade early-stage endometrial cancer patients to come back for a follow-up visit near one month. Consequently, pain data at near 2 weeks provided richer and more robust information for high-risk gynecological cancer patients, which led us to favor using pain at 2 weeks as an outcome for analysis in our study. Furthermore, based on the updated definition of CPSP based on International Classification of Diseases 11th Revision (ICD-11), which is pain lasting for 3 months after surgery(Korwisi et al., 2022), we intended to use the term "persistent post-surgical pain" in rather than CPSP to describe our research findings more accurately.

2.1.5 Data analyses

Building upon a detailed data collection process, we recoded variables such as marital status, diagnosis, smoking, cancer stage, and surgery procedures, aligning them with the common categorizations found in existing literatures. The details of reclassifications can be found in Manuscript #2 and Manuscript #3.

For Aim 2, although our initial plan was to use logistic regression to assess the predictive value of the acute pain trajectory for the presence of pain at 1- and 2-months post-surgery, we realized that this approach would oversimplify the nuanced spectrum of persistent postsurgical pelvic pain, which is scored from 0 to 10 based on NRS. To capture the characteristics of persistent pain more accurately, we decided to implement generalized linear models for all outcome variables including persistent pain, 30-day readmission and prolonged opioid use.

Now revised data analysis for Aim 2:

Aim 2.1 To evaluate the bivariate correlations between acute pain trajectories and the development of chronic pain, 30-day readmission and prolonged opioid use, Chi-Square tests will be used to determine whether there is a significant association between the categories of acute pain trajectories and the outcomes. The hypothesis posits associations between the acute pain trajectories and the development of chronic pain, 30-day readmission and prolonged opioid use. A p-value of $< .05$ indicates statistical significance.

Aim 2.2 To delineate the relationships between acute pain trajectories and the development of chronic pain, 30-day readmission and prolonged opioid use adjusting for the covariates, generalized linear models (GLMs) will be utilized. The primary independent variable will be acute pain trajectory group membership. Potential confounding variables such as age, BMI, diagnostic category, surgical procedure, ASA class, presence of an anxiety diagnosis, receipt of neoadjuvant chemotherapy, preoperative opioid use, and preoperative pelvic pain will be controlled for in the models. These covariates will be selected based on clinical relevance and potential to confound the relationship between pain trajectory and outcomes(Chapman et al., 2011b, 2011a, 2012; Imai et al., 2021). Prior to GLMs, univariate analyses will be conducted to identify variables significantly associated with the outcomes. Continuous variables will be assessed using t-tests or Wilcoxon rank-sum tests if non-normality is present. Categorical variables will be assessed using Chi-square or Fisher's exact tests as appropriate. Variables with a p-value less than 0.25 in univariate analyses will be considered for inclusion in the multivariable models. Odds ratios with 95% confidence intervals will be computed to estimate the relative risk of the outcomes associated with each acute pain trajectory, adjusted for other covariates in the model.

2.2 CONCLUSIONS, IMPLICATIONS FOR NURSING, AND FUTURE STUDIES

This dissertation study comprehensively investigated post-surgical pain following hysterectomy for gynecologic cancer with three distinct focal points, producing noteworthy conclusions and implications for nursing:

The first manuscript addressed CPSP, revealing considerable variation in incidence rates post-hysterectomy, which were between 10% and 50% at 2-3 months and tended to decrease over time. Key risk factors for CPSP were identified as presurgical pelvic pain, high acute postoperative pain, pain catastrophizing, and presurgical anxiety. The study highlighted the complex nature of CPSP, noting that assessment methods (including the follow up assessment timepoints and CPSP definitions [i.e., greater than 0 on a 0-10 scale vs. greater than 3 on a 0-10 scale]) contribute to incidence variability and emphasize the importance of a comprehensive approach that accounts for pain type, characteristics, and pain interference, particularly in gynecological cancer patients.

The second manuscript focused on the dynamic nature of APSP, identifying four distinct pain trajectories within five days following hysterectomy for gynecologic cancer. Notably, while most patients experienced no pain or rapid pain resolution (73%), a significant portion endured slow resolution or ongoing pain (25%). Factors associated with membership in the ongoing pain trajectory included presurgical anxiety, presurgical pain, open hysterectomy, ASA Class>=3, and higher comorbidity scores. The second manuscript emphasizes the necessity for nurses and other clinicians to adopt individualized pain management strategies for patients with gynecologic cancer undergoing hysterectomy. Nurses should conduct thorough preoperative assessments, with a focus on chronic pelvic pain and preoperative anxiety, to identify patients at higher risk for ongoing postoperative pain. In terms of tailored pain management to meet the complex need of cancer

patients, although patient-controlled analgesia (PCA) pumps have traditionally been the standard for postoperative pain management, recent research advocates for a multimodal approach. The approach combines standard opioids with non-opioid approaches like anti-inflammatory agents, nerve blocks, N-methyl-D-aspartate antagonists such as dextromethorphan, magnesium, gabapentin, and acetaminophen (Azari et al., 2013). Notably, even patients with higher ASA class, indicating a greater health burden, have shown potential benefits from multimodal pain management approaches, with some experiencing earlier discharges compared to those managed conventionally (Santoso et al., 2014). Future research should investigate the effectiveness of novel approaches for managing the dynamic and evolving aspects of postoperative pain.

The third manuscript explored the link between APSP trajectories and long-term postoperative outcomes in high-risk gynecologic cancer cases. Unlike findings from manuscript # 2, a significant number of patients (50%) in this high-risk sample were categorized into the slow resolution and ongoing pain trajectories, highlighting the need for persistent pain management and early intervention strategies for patients with high-risk gynecological cancer. The study confirmed that distinct pain trajectories could predict persistent pain, 30-day readmission rates, and prolonged opioid use, although in multi-variate analysis, acute pain trajectory membership did not predict prolonged opioid use. Acknowledging the strong associations between acute pain experiences and longer-term outcomes, clinical care must focus on both immediate and extended postsurgical care to enhance recovery and reduce the risks of chronic pain and opioid dependency. Nurses play a critical role in monitoring pain, understanding its patterns, and advocating for individualized pain management strategies. Future research could explore the development of a nurse-led pain management program to determine the most effective clinical practices for delivering individualized and continuous care post-hysterectomy. This initiative would aim to refine pain

monitoring techniques, tailor pain interventions based on patient-specific trajectories, and extend the scope of nursing care to address both immediate and long-term postoperative challenges.

Furthermore, the study relied on retrospective information obtained from medical records and the ERAS dataset, which did not allow for a comprehensive assessment of socioeconomic status and other psychological factors. Future studies should also include prospective designs that incorporate a more comprehensive assessment of psychological factors, socioeconomic status, and a more detailed evaluation of anxiety and preoperative pain. Investigations in a variety of clinical settings across different hospitals would also help in validating the findings. Moreover, to capture the complexities of postoperative pain, future research should aim for more detailed pain assessments at varied time intervals and differentiate between types of pain (e.g., movement vs. rest, average vs. peak pain). This would offer a nuanced understanding of pain trajectories and their management. Additionally, a deeper examination about the transition from APSP to persistent pain should be pursued. These efforts will likely provide a more robust framework for developing clinical interventions that can be tailored to individual patient experiences and needs.

Furthermore, the investigation into the moderating effects of covariates on the relationship between APSP trajectories and the development of persistent pain, readmission rates, and prolonged opioid use—initially addressed as Aim 3—has been preliminarily presented in Appendix D, Supplementary Tables 2 to 6. These foundational findings could be expanded upon and form the core of Manuscript #4 for this dissertation study.

The research illuminates the complex dynamics of post-surgical pain, underscoring the variability in individual pain experiences and recovery trajectories. Crucially, the findings advocate for personalized pain management approaches tailored to patient-specific factors. These

insights are instrumental in informing clinicians and improving postoperative care protocols, especially for those with high-risk gynecologic cancers.

3.0 MANUSCRIPTS

3.1 DISSERTATION MANUSCRIPT 1: REVIEW OF LITERATURE

Risk factors for and Assessment of Chronic Post-surgical Pain Following Hysterectomy for Benign and Malignant Conditions: A Review of the Literature

3.1.1 Abstract

Chronic post-surgical pain (CPSP) following hysterectomy has emerged as a significant concern, especially in the context of gynecologic cancer, impacting the quality of life. Extending previous reviews, this study encompassed patients with both benign and cancer diagnoses undergoing hysterectomy. Objectives were to (1) synthesize key findings on CPSP incidence and associated risk factors, (2) present the influence of diverse CPSP definitions and assessment methodologies on reported incidence rates, and (3) determine the consistency in potential risk factors of CPSP across multiple studies. Drawing from 877 initial papers sourced from PubMed, Web of Science, and CINAHL, 17 met inclusion criteria. Results indicated that CPSP incidence rates exhibits considerable variation, ranging from 10% to 50% at 3 months, gradually declining over time. Dominant risk factors included preoperative pelvic pain, acute postoperative pain intensity, pain catastrophizing, and presurgical anxiety. Variability in CPSP incidence, even after adjusting for different assessment methods, highlights the complex nature of CPSP. The multifaceted nature of CPSP necessitates a comprehensive approach, encompassing not only pain

intensity but also its type, characteristics, and impact on daily life, especially considering the emotional dimension in cancer patients.

3.1.2 Introduction

Chronic postsurgical pain (CPSP), which is usually defined as pain lasting for 2 months after surgery, is a common problem after hysterectomy for gynecologic cancer and can have a major impact on function and quality of life. In 2023 an estimated 66,200 people in the United States will be diagnosed with uterine or endometrial cancer; 13,960 will be diagnosed with invasive cervical cancer, and an estimated 19,710 people will be diagnosed with ovarian, fallopian tube, and peritoneal cancer(Siegel et al., 2023). Hysterectomy, or surgical removal of the uterus, is commonly used in the treatment of gynecologic cancers, and most patients experience acute postsurgical pain (APSP) that resolves within 1-2 weeks. However, CPSP can progress to APSP in 12%-50% of patients undergoing hysterectomy, irrespective of surgical success(Brandsborg et al., 2007; Honerlaw et al., 2016a).

CPSP significantly increases the incidence of depression, anxiety, insomnia, and other health problems, which not only brings suffering to patients, but also creates millions of dollars in excess medical expenditures(Nadeau et al., 2021). According to epidemiological surveys, more than 100 million adults in the United States alone suffer from chronic pain each year, and the annual direct (treatment costs) and indirect (productivity loss) economic losses due to pain are as high as $650 billion, far more than any other economic losses due to disease(Gaskin & Richard, 2012). Since a proportion of patients develop chronic pain after hysterectomy, it is imperative to identify high-risk individuals to effectively prevent the occurrence of severe postoperative chronic pain.

A review by Brandsborg (2018) provided crucial insights into the prevalence of chronic post-surgical pain following hysterectomy in patients with benign conditions and found that chronic pain is reported by 5-32% of women after hysterectomy(Brandsborg & Nikolajsen, 2018a). Our review aims to extend and deepen this work in three keyways. First, this review will broaden the scope of investigation to include patients with cancer diagnoses. More extensive surgeries as well as post-operative radiation therapy and/or chemotherapy could put patients with cancer at higher risk for CPSP after hysterectomy. This inclusion allows for a more comprehensive understanding of CPSP after hysterectomy. Second, this review focuses on the methodologies used to define CPSP incidence which varies greatly (10% to 50%) across studies (Brandsborg & Nikolajsen, 2018b). We aim to classify data on incidence according to assessment times and the definition of CPSP based on pain intensity levels. This process could provide important information for standardizing measurements, enabling more accurate comparisons across studies, and help identify best practices in assessment. Finally, we will conduct a detailed exploration of findings related to all evaluated risk factors for the development of CPSP. Instead of the purely descriptive approach used by Brandsborg, our research will provide a more quantifiable view of the various risk factors for CPSP. This combination of expanded patient groups, concentrated focus on methodology, and statistical approach to evaluate risk factors distinguishes this review from others, providing an opportunity to glean more nuanced and actionable insights into CPSP after hysterectomy.

Therefore, the purpose of the study is to:

1) Identify and extract key features of research studies evaluating the incidence and risk factors of chronic post-surgical pain after hysterectomy, including both benign and malignant conditions.

2) Present the influence of the published CPSP assessment methods, including the follow up assessment timepoints and CPSP definitions [i.e., larger than 0 out of a 0-10 scale], on reported CPSP incidence rates.
3) Evaluate the consistency of findings related to potential risk factors of CPSP across multiple studies (frequency of statistical significance for all potential risk factors evaluated in 2 or more studies of CPSP).

3.1.3 Methods

Our literature review, spanning publications from 2007 to July 2023, builds upon Brandsborg's 2018 study which concentrated on CPSP articles post-hysterectomy up to 2007(Brandsborg & Nikolajsen, 2018b, 2018a). We sourced publications from three databases that are repositories of health and science research papers: PubMed, Web of Science, and CINAHL.

The initial search strategy applied broad search terms to ensure a comprehensive sweep of relevant literature. We combined the keywords 'chronic pain' or 'persistent pain' with 'hysterectomy', aiming to capture any article discussing long-term pain post-hysterectomy. We purposefully did not include 'post-operative pain' in our initial search to avoid limiting our results to immediate post-operative studies, aiming instead to capture a wider range of articles that encompassed longer-term pain experiences.

Following the initial search, we imported all resulting articles into the reference management software, EndNote. This consolidation allowed for an efficient and organized review process. We systematically screened the articles by examining titles and abstracts, filtering out irrelevant publications and identifying potential articles for full-text review. The inclusion criteria required

that the studies 1) involve patients who were 18 years or older and who had undergone a hysterectomy and 2) include incidence of CPSP as primary outcome. Studies were excluded if they 1) involved non-human subjects, 2) included non-adults (under 18 years old), 3) were published in languages other than English, 4) were case studies, reviews, or protocols and RCTs comparing different pain management strategies, and 5) did not report the incidence of CPSP.

3.1.4 Results

The initial database search yielded a total of 877 studies. Following the removal of duplicates, 646 unique studies remained for consideration. After a thorough review, 17 studies were deemed to meet all inclusion criteria and were included in our final review. The screening process is depicted in **Manuscript 1 Figure 1**.

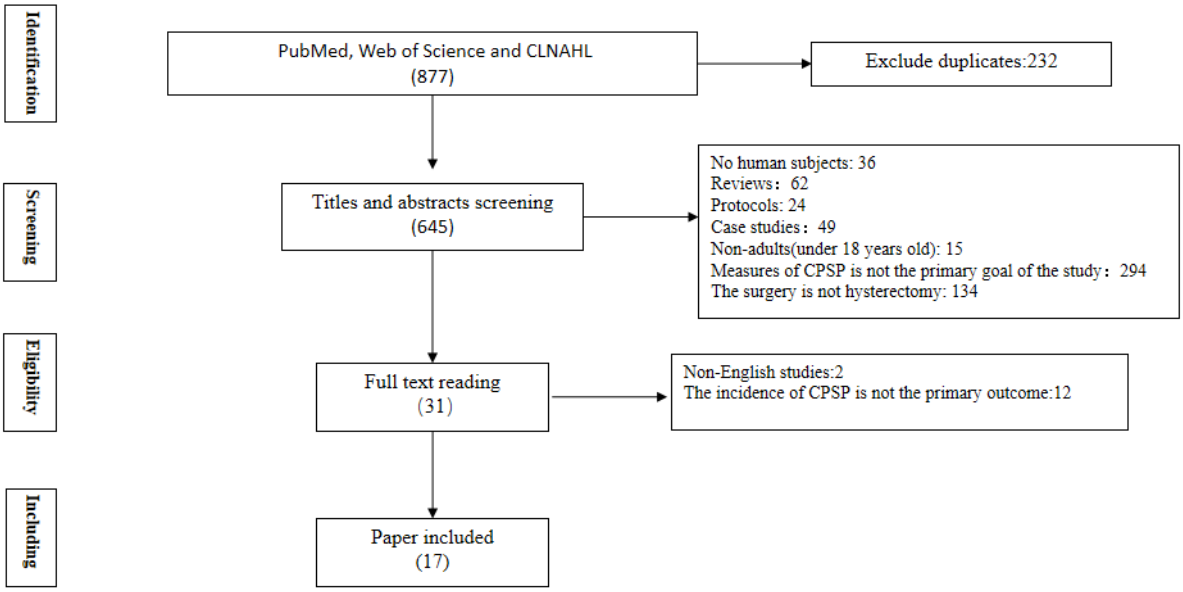
Both prospective and retrospective studies were represented, with sample sizes ranging from 21 (Saxena et al., 2016)to 1299 participants (Brandsborg et al., 2007). The methods of measuring CPSP varied across studies, but a common method was the use of a numeric rating scale or a YES/NO question about the existence of CPSP. Different time thresholds were used to define CPSP, varying from 3 months to over 5 years post-surgery. CPSP incidence varied greatly across studies, ranging from as low as 4.1% (Montes et al., 2015)to as high as 50%(Pinto et al., 2012). The review found 3 studies of CPSP after hysterectomy specific to cancer with the incidence of CPSP ranging from 11.9% to 38.1%.

To evaluate the influence of CPSP assessment methods, we compared the incidence of CPSP based on follow-up assessment timepoint and Numeric Rating Scale (NRS) severity level.

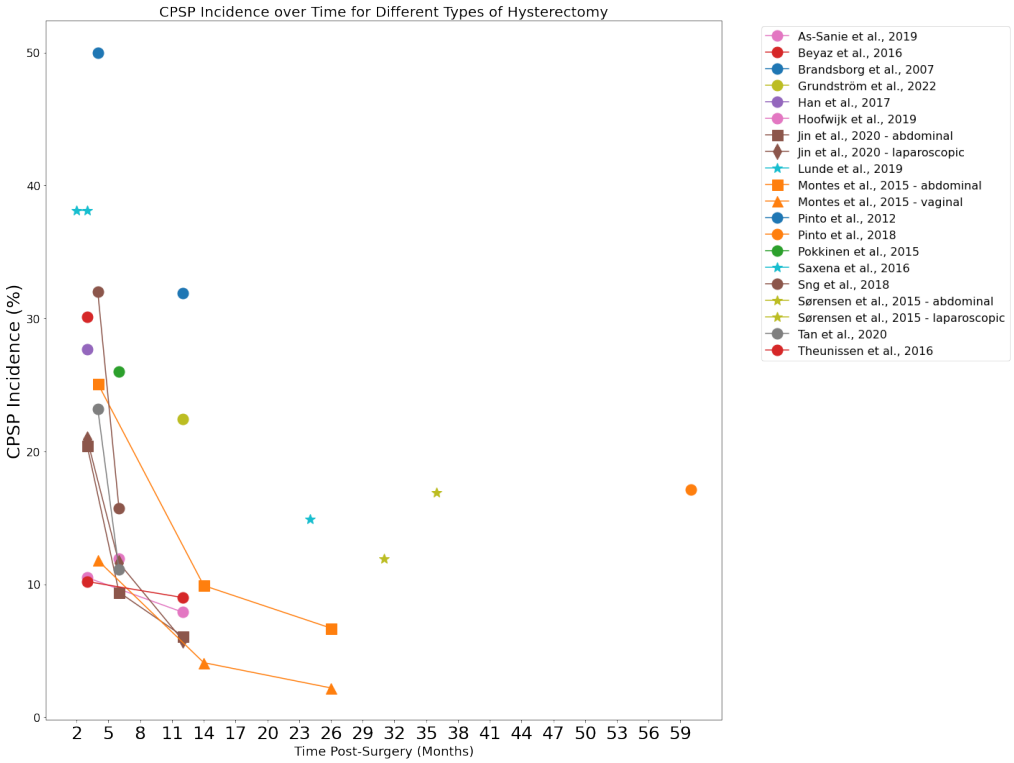
Manuscript 1 Figures 2 and **3** includes the CPSP ranges over included study assessment times and different CPSP definitions respectively. Figure 2 depicts a general trend indicating a decrease in chronic post-surgical pain (CPSP) incidence as follow-up time increases. However, CPSP was documented to persist up to five years post-hysterectomy. A majority of studies focused on assessing CPSP within a range of 3 to 12 months post-surgery, with the most frequent assessment occurring at 3-months post-surgery. The CPSP incidence reported at this 3-month assessment varied widely, from 10% to 50%.

In Figure 3, the review analyzed the incidence of CPSP based on different CPSP definitions. A common definition for CPSP is that any reported pain (either a score above 0 on a 0-10 NRS scoring or a simple YES to a pain question) was classified as CPSP. Surprisingly, even with this lenient definition, there was a broad range in reported incidences, ranging from 2.2% to 50%. When stricter cut-off values, like 3 or 4, were employed to represent more severe pain, the reported incidence of CPSP was generally lower. However, Saxena et al.'s 2016 study on ovarian cancer patients was an outlier, showing a high incidence even with these stringent cut-off values(Saxena et al., 2016).

All the potential risk factors explored in two or more the studies included in this review were extracted and reported in **Appendix B**. **Manuscript 1 Figure 4** provides a visual summary of the most common risk factors associated with CPSP, as identified in the literature specific to hysterectomy. The most commonly identified significant risk factors for CPSP were preoperative pelvic pain, acute postoperative pain intensity (at movement), pain catastrophizing, and presurgical trait anxiety.

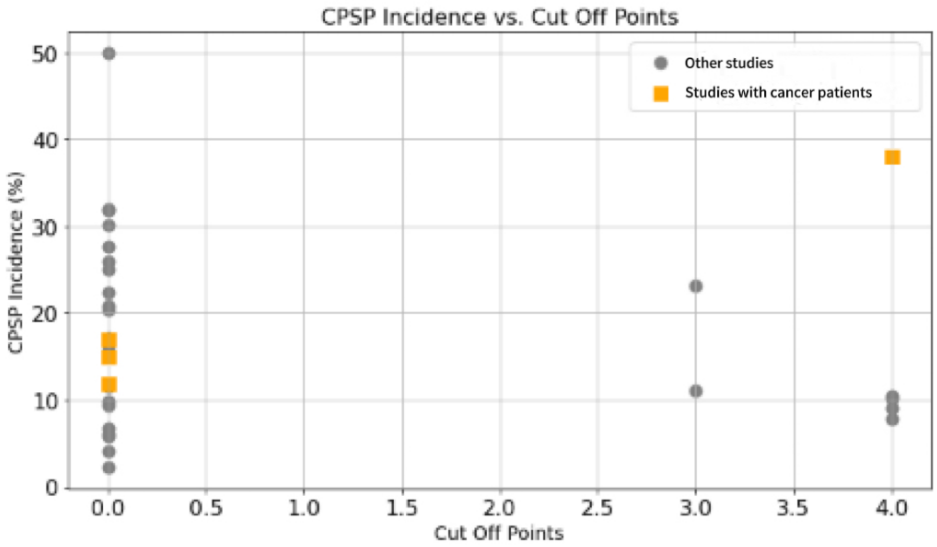


2 Manuscript 1 Figure 1 The screening process of papers

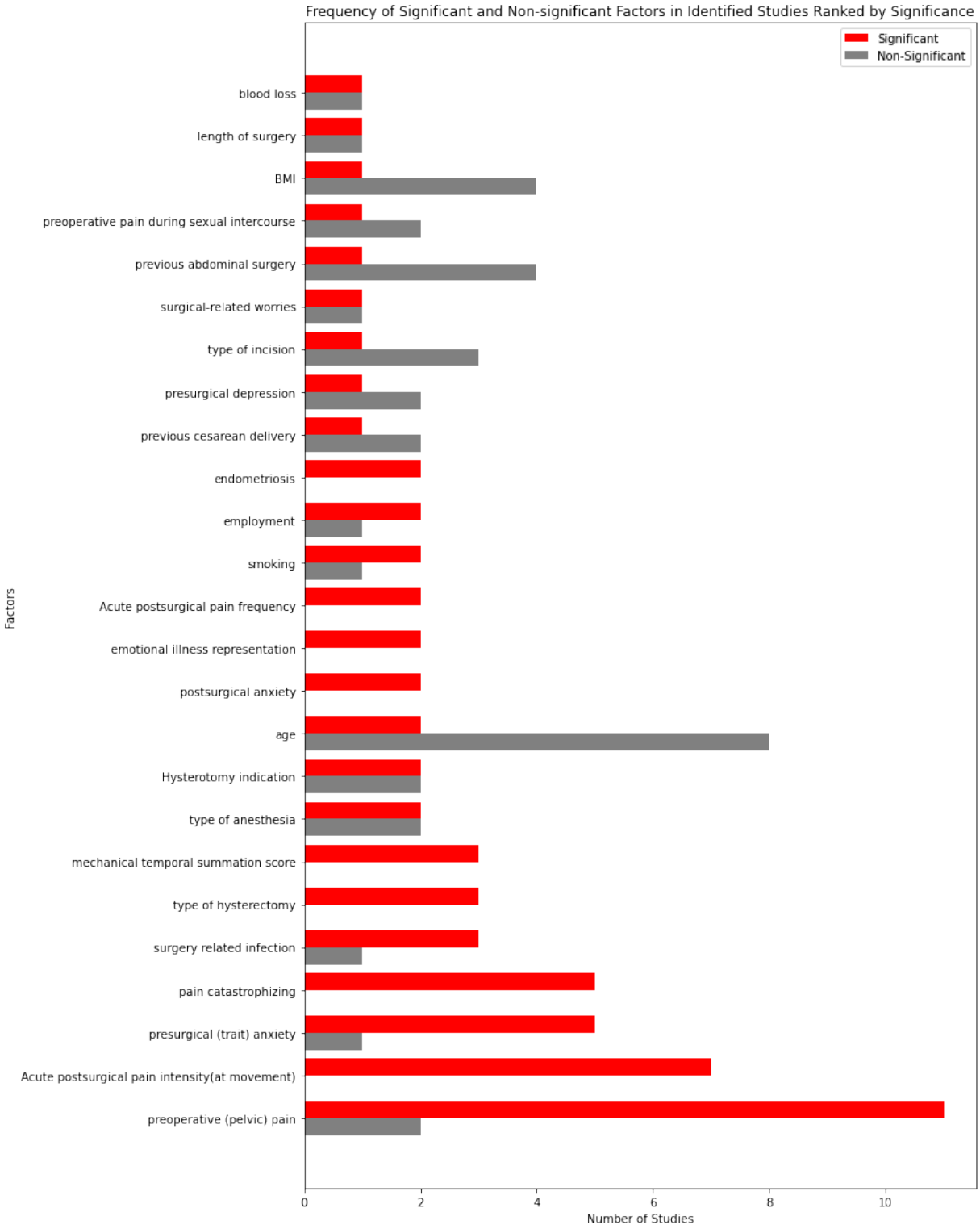


3 Manuscript 1 Figure 2 Chronic Post-Surgical Pain (CPSP) rate over time across different studies

Manuscript 1 Figure 2: This line plot represents the Chronic Post-Surgical Pain (CPSP) rate over time across different studies. Each line corresponds to a different study, with different colors representing different studies. The markers along each line represent the CPSP rate at different months after surgery. Studies among cancer population are marked as stars**.**



4 Manuscript 1 Figure 3 CPSP rate for different CPSP definitions across different studies



5 Manuscript 1 Figure 4 Frequency of Risk Factors Identified in Studies Associated with Chronic Post-Surgical Pain (CPSP) after Hysterectomy

Manuscript 1 Figure 4 Factors from **Appendix B** that were investigated two times or fewer, and found to be non-significant, are excluded from Figure 4. The horizontal bar chart represents the frequency at which different risk factors have been identified across multiple studies.

Significant predictors evaluated in only one study include disease onset, long term consequences of surgical fear, intraoperative morphine consumption, rs4818(COMT gene), uterine fibroids, bleeding complication, micturition complications, preoperative heat pain hyperalgesia, Up-regulation in the mRNA expression of signal transduction genes.

3.1.5 Discussion

In summary, our review identified 17 studies exploring chronic post-surgical pain (CPSP) after hysterectomy, for both benign and malignant conditions. The review provides a comprehensive report and visualization of the published data on CPSP incidence, organizing it according to different assessment time points and pain cut-off values. This approach revealed an overall trend of decreasing CPSP over time. It also underscored the considerable variation in reported incidence rates, emphasizing the need for standardized measurement practices. The review further delved into the risk factors associated with CPSP, providing a side-by-side comparative horizontal bar chart of various factors related to studies, delineated based on their significance. This methodology is a departure from earlier literature reviews ((Brandsborg & Nikolajsen, 2018a)) and offers a more quantifiable perspective on the CPSP risk landscape.

As a result, the review found CPSP incidence at 3 months post-hysterectomy ranged from 10% to 50%. For those studies that assessed CPSP at multiple timepoints, a decreasing trend in CPSP incidence over time is evident. Currently, most research evaluates CPSP within the 3 to 12 months

post-surgery period. However, we found only one study that assessed CPSP 5 years post-hysterectomy (incidence rate of 17.1%), suggesting that more evidence is needed to better understand prolonged CPSP(Pinto, McIntyre, Araujo-Soares, et al., 2018). For studies using a simple metric of CPSP--any reported pain (either a score above 0 on a 0-10 NRS scoring or a simple YES to a pain question) was classified as CPSP--the CPSP incidence ranged broadly from 2.2% to 50%.

The significant variability in reported CPSP incidence, even when accounting for distinct CPSP definitions and assessment periods, underscores the multifaceted nature of CPSP research. Currently, the Numeric Rating Scale (NRS) is the predominant tool used for CPSP assessment. The advantages of the NRS include its simplicity and ease of use, making it accessible to a wide range of patients. Furthermore, its linear format provides a clear gradient of pain intensity, facilitating consistent communication between patients and healthcare providers about the severity of pain. However, the scale relies heavily on patients' self-reported pain levels, which can be influenced by various external factors, for example, moods, time of recall, or even cultural perceptions of pain. Furthermore, it does not capture the multifaceted experience of pain, including its duration, type, or the emotional distress it may cause(Hjermstad et al., 2011; van Ransbeeck et al., 2018). Conversely, some studies employed a straightforward YES/NO response to a CPSP-related question. This approach has the advantage of being unambiguous in nature, eliminating any potential confusion or over-analysis by patients. It provides a clear binary distinction, making data collection and analysis more straightforward. However, this binary method also introduces similar disadvantages to the NRS(van Ransbeeck et al., 2018). A simple YES/NO answer doesn't provide insights into the severity, type, or frequency of the pain, which can be crucial for clinical assessments and interventions.

The assessment of acute post-surgical pain (APSP) was comprehensive in most of the studies, as reflected in studies like Pinto 2012, which included both frequency and intensity of APSP; Han et al., 2017, which examined pain at movement and rest; Sng et al., 2018, focusing on the pain experienced during specific activities like coughing and itching; and Tan et al., 2020, which assessed the location of the pain. These nuanced evaluations paint a detailed picture of APSP, aiding in its effective management. Yet, the assessment of chronic post-surgical pain (CPSP) was notably less detailed, leaving us with a vague understanding. Cancer patients, in particular, are a demographic that would greatly benefit from a more in-depth examination of CPSP. For these patients, the persistence of pain months after surgical procedures isn't just a matter of physical discomfort but can also have profound influence on their psychological well-being and quality of life. Moreover, cancer therapies, such as chemotherapy or radiation, can complicate the pain experience, further underscoring the need for a detailed evaluation of CPSP.

When considering CPSP assessment especially for cancer patients, several facets need deeper exploration. First, it's essential to assess more than just presence or intensity of pain, examining the nature and characteristics of the discomfort. This entails discerning the type of pain, whether it's neuropathic or nociceptive, and understanding its frequency and potential triggers to present a comprehensive picture. Second, the impact of CPSP on daily life needs to be determined. It's imperative to assess its influence on activities of daily living, sleep quality, and overall quality of life. The emotional dimensions of CPSP are another critical aspect. Given the mental stressors associated with a cancer diagnosis, gauging the emotional influence of CPSP, particularly its relationship with anxiety or depression, is vital. Furthermore, the importance of detailed, regular follow-ups, especially for cancer patients, is paramount. Such follow-ups provide a mechanism to monitor the progression or possible relief of CPSP, delivering crucial insights into its long-term

trajectory and pain management. Lastly, understanding the interplay between CPSP and other cancer treatments is necessary. Recognizing how treatments, such as chemotherapy or radiation, may exacerbate or influence CPSP is also important in formulating effective pain management strategies.

Risk factors for CPSP

The commonly identified significant risk factors for CPSP were preoperative pelvic pain, acute postoperative pain intensity (at movement), pain catastrophizing, and presurgical trait anxiety. These findings are consistent with many earlier studies which suggest that psychological factors and perioperative pain are major predictors of CPSP(Pinto et al., 2012; Pinto, McIntyre, Araujo-Soares, et al., 2018; Tan et al., 2020).

Psychological factors were consistently identified as significant risk factors for CPSP in multiple studies. Preoperative anxiety and pain catastrophizing were among the most frequently observed psychological factors associated with CPSP(Pinto, McIntyre, Araujo-Soares, et al., 2018; Sng et al., 2018c; Tan et al., 2020). The results suggest that preoperative psychological assessment and intervention might be important in identifying and supporting patients at risk of developing CPSP.

Other identified risk factors were less consistently noted across studies. Age was found to be significant in some studies(Pinto et al., 2012; Sng et al., 2018a), while others found no significant association suggesting that the influence of age on CPSP may be context dependent(Beyaz, Ozocak, et al., 2016; Han et al., 2017). Similarly, BMI was not a significant factor in most studies, while it was identified as a significant risk factor for post-surgical pain at 1 year in a study where participants had a BMI of 25 kg/m^2 or higher in univariate analysis(Grundström et al., 2022). The association of smoking with an increased risk of CPSP is consistent with literature indicating

that smoking can negatively affect surgical outcomes and pain levels, likely due to its impact on the body's inflammatory and healing processes(Stienen et al., 2014).

Some CPSP risk factors were related to surgical factors. Several studies found that the type of hysterectomy was a significant surgical-related risk factor for CPSP. For example, Grundström et al. (2022) reported that certain types of hysterectomy (i.e., abdominal and laparoscopic) were associated with a higher risk of CPSP compared to vaginal hysterectomy. Identifying the specific hysterectomy techniques that contribute to CPSP can help guide surgical decision-making and potentially reduce the incidence of chronic pain after surgery. Additionally, the mode of anesthesia was identified as a significant factor by Theunissen et al. (2016), emphasizing the potential role of anesthesia management in mitigating CPSP risk. The type of incision used during surgery (i.e., Pfannenstiel incision) was also shown to be significant in some studies(Pinto, McIntyre, Araujo-Soares, et al., 2018; Tan et al., 2020).

Perioperative pain was consistently identified as significant risk factors for CPSP across various studies. Preoperative pelvic pain was strongly associated with CPSP(Hoofwijk et al., 2019; Pinto et al., 2012; Pinto, McIntyre, Araujo-Soares, et al., 2018). Addressing and managing preexisting pain conditions before surgery might be critical in reducing the risk of CPSP. Acute postsurgical pain intensity and frequency were also significant predictors of CPSP (Pinto et al., 2012, 2018; Tan et al., 2020). What we found is consist with Brandsborg's review and numerous studies from other fields about acute postsurgical pain and CPSP. The mechanism underlying the transition from acute pain to CPSP has not been fully explored. One possible argument is that the chronification of pain after surgery takes place at the periphery, whereby repeated nociceptive messaging during the acute pain phase strengthens the synaptic connections between nociceptive afferents and the spinal cord neurons that engage in noxious signaling, and the result is

hyperalgesia(Chapman & Vierck, 2017; Glare et al., 2019). Persistent noxious signaling could cause maladaptive neuroplastic changes in brain function and structure to sustain treatment resistant chronic pain(Burke & Shorten, 2009; Pergolizzi et al., 2014). Additionally, the presence of mechanical temporal summation (MTS) and evoked MTS were highlighted as significant predictors of CPSP (Sng et al., 2018; Tan et al., 2020). These findings suggest that assessing pain processing patterns before surgery might aid in identifying patients at higher risk of developing CPSP.

In the three studies of patients with cancer, only Lunde explored cancer stage as a predictor of CPSP and did not find a significant association with the incidence of CPSP. However, most of the patients in these studies had early-stage endometrial cancer; only 21 patients had advanced cancer across the three studies. This might explain why the severity of cancer stage did not prove to be a significant factor(Saxena et al., 2016). Also, according to the study from Saxena (2016), higher incidence (38.1%) of CPSP for ovarian carcinoma could be attributed to the use of a larger midline incision, and extensive tissue handling may have contributed to nerve injury.

Collectively, these findings specific to CPSP risk factors suggest that a more comprehensive, biopsychosocial model might be needed to accurately predict and prevent CPSP in individuals undergoing hysterectomy. Strategies for controlling CPSP might include better management of pre- and postoperative pain, psychological support for patients showing high levels of anxiety or pain catastrophizing, and a focus on optimizing health factors like smoking cessation(Grundström et al., 2022; Pokkinen et al., 2015).

Despite these important findings, there are several limitations to this review. For instance, the studies varied greatly in their methodologies, which impacts the consistency and generalizability of findings. Furthermore, observational studies about cancer patients cannot definitively prove

causation. While reported risk factors were associated with CPSP, further research is required to confirm directionality and strength of these relationships. To address knowledge gaps identified in this review, future studies should seek to standardize CPSP definitions and outcomes, use longitudinal designs to track changes over time, and consider potential interactions between risk factors.

3.1.6 Conclusion

This comprehensive review offers a deeper understanding of chronic post-surgical pain (CPSP) after hysterectomy, spanning both benign and cancer conditions. The findings underscore the need for standardized measurement practices, given the considerable variation in CPSP incidence. With perioperative pain, psychological factors, and specific surgical techniques consistently emerging as significant predictors, there's a clear call for a holistic, biopsychosocial approach in the management and prediction of CPSP. The results further emphasize the importance of optimizing patient health pre-surgery, offering psychological support where needed, and ensuring effective pain management strategies post-surgery. However, the varied methodologies across studies signal a caveat. Future research should aim for methodological consistency, considering the interactions between risk factors and employing longitudinal designs to provide clearer insights into the evolution of CPSP over time.

3.2 DISSERTATION MANUSCRIPT 2: APSP TRAJECTORY STUDY

Acute Post-Operative Pain Trajectories in Gynecological Cancer Patients Undergoing Hysterectomy

3.2.1 Abstract

Background: Although acute post-surgical pain (APSP) after hysterectomy is dynamic , it is often operationalized as a static variable in analyses of predictors and outcomes of APSP. There is limited research on APSP trajectories, or changes over time, particularly after hysterectomy for gynecologic cancer. Research on APSP trajectories could reveal patterns of change in pain intensity and improve our ability to tailor postoperative pain management.

Objective: This study aimed to 1) identify distinct APSP trajectories for five days following hysterectomy in patients with gynecologic cancer and 2) evaluate factors associated with membership in the distinct pain trajectories.

Methods: The study used an Enhanced Recovery After Surgery (ERAS) dataset combined with medical records review. The combined dataset encompassed demographic details, medical comorbidities, pathologic findings, surgical techniques, and postoperative pain experiences. The study examined APSP trajectories in adult patients diagnosed with gynecologic cancer who underwent minimally invasive or open hysterectomy between January 1, 2019, and December 31, 2021. Group-based trajectory modeling was used to characterize acute pain patterns post-surgery. Factors associated with APSP trajectories were identified using multinomial regression models.

Results: Results: 1342 patients with a confirmed gynecologic cancer diagnosis were eligible for the study. Group-based trajectory modeling identified four distinct pain trajectory groups post-surgery: 1) 10% reported no pain, 2) 63% had rapid pain resolution, 3) 16% had slow resolution, and 4) 9% had ongoing pain up to five days post-surgery. Several factors were associated with a heightened likelihood of being in the ongoing post-operative pain trajectory group: having a prior anxiety diagnosis, presenting with preoperative pelvic, undergoing open hysterectomy, and possessing a higher American Society of Anesthesiologists Classification (ASA Class). Patients with higher Charlson Comorbidity Index (CCI) scores and longer surgical duration had reduced odds of belonging to the no pain or quick resolution groups compared with ongoing pain.

Conclusion: While most patients witnessed APSP resolution within four days of the hysterectomy, a notable subset battled prolonged pain, underscoring the imperative for individualized pain management. By tailoring care plans, encompassing medical and psychiatric histories, enhanced pain management and recovery can be achieved. Further research might elucidate the potential long-term implications of persistent APSP.

3.2.2 Introduction

Gynecological cancers are a significant public health concern, with the American Cancer Society estimating that in 2023, 66,200 individuals in the United States would be diagnosed with uterine (including endometrial) cancer, 13,960 with invasive cervical cancer, and 19,710 with ovarian, fallopian tube, or peritoneal cancer. Hysterectomy, the surgical removal of the uterus, is a common treatment for these cancers.

Acute postoperative pain (APSP), defined as an unpleasant, complex, and dynamic psychophysiological response to tissue trauma or acute inflammatory processes, is an inherent part of the immediate post-surgical experience following hysterectomy (Chapman & Vierck, 2017). Although many patients experience APSP that resolves within 1-2 weeks, this pain can have far-reaching consequences including prolonged hospital stays, increased medical expenses, and a higher risk of severe postoperative cardiovascular and thrombosis-related complications (Gan, 2017). If uncontrolled, this acute pain can transition into chronic pain, negatively impacting the patient's health(Katz & Seltzer, 2009; Theunissen et al., 2017; VanDenKerkhof et al., 2012).

Despite the significant impact of APSP on patient outcomes, gaps persist in our understanding of the dynamics and determinants of APSP following hysterectomy for gynecologic cancers. The most common sociodemographic/lifestyle, medical history, and peri-operative risk factors are summarized below; however, studies are often limited in scope and sample size.

Sociodemographic/lifestyle factors: Age and body mass index (BMI) are prominently highlighted in APSP research. Studies such as those by van Ransbeeck et al. (2018) and Wang et al. (2018) show that younger patients typically report greater APSP intensity. On the other hand, some research, like the findings of Won et al. (2018), shows no significant correlation between age and APSP. The relationship between BMI and APSP presents a U-shaped curve. Specifically, women at the extremes, either with a BMI of 30 or above or 20 or below, are at a heightened risk of APSP (Osler et al., 2011). Other factors meriting attention include preoperative smoking status, education level, and race. However, comprehensive research on these factors, especially in the context of hysterectomy, remains scarce (Jin et al., 2020; Sng et al., 2018b).

Psychological Risk Factors: The intersection of psychology and APSP predominantly revolves around anxiety, depression, and pain catastrophizing. The role of anxiety is particularly

noteworthy due to its potential to influence pain perception through descending pathways(Tseng et al., 2017; van Boekel et al., 2021). Previous findings also suggest that trait anxiety affects postoperative pain by influencing preoperative state anxiety(Kain et al., 2000). While links between preoperative anxiety and APSP are known, they are often presented as linear relationships in research, making it difficult to precisely identify which particular patients that needs psychological intervention to prevent APSP.

Medical History Factors: Several aspects of a patient's medical history can be predictive of APSP. Notable among these could be specific diagnosis, the stage of cancer if present, the Charlson Comorbidity Index (CCI), and any record of previous pelvic or abdominal surgeries(Brandsborg, 2012b; Pinto et al., 2012).

Perioperative Factors: The state of a patient's pain before the surgery and their history with opioids can be indicative of their post-surgical pain experience. Those with preoperative pain or a history of opioid use frequently report higher APSP scores (Menendez et al., 2018). The nature of the surgical procedure itself can also be a determinant. Surgeries like large joint orthopedics, thoracic procedures, and abdominal hysterectomies are often linked to elevated postoperative pain levels (Gerbershagen et al., 2013). However, the relationship between the duration of the surgical procedure and postoperative pain, specifically after abdominal hysterectomies, remains underexplored. Given the typically traumatic nature of extended, cancer-related surgeries, further studies are crucial to fully understand the interplay between surgical duration and APSP, especially for gynecological cancer patients.

Moreover, APSP after hysterectomy is often operationalized as a static variable, despite being a dynamic process. Summarizing APSP as either a snapshot of a single timepoint or an average of multiple assessments over time may overlook important attributes such as changes in APSP over

the acute recovery period (Chapman, Donaldson, et al., 2011a; Chapman, Donaldson, et al., 2011b; Chapman et al., 2012). Group-based trajectory modeling (GBTM) offers a potentially promising approach for classifying the progression of APSP, but its application to hysterectomies is also limited, signifying a considerable gap in our understanding of APSP trajectories after this procedure (Okamoto et al., 2018).

This research intends to address these gaps by 1) determining distinct post-operative acute pain trajectories over five days following hysterectomy for gynecologic cancer, and 2) evaluating factors associated with distinct trajectory membership. By utilizing group-based trajectory models and multinomial regression models, we aim to provide a comprehensive understanding of APSP and contribute to a better understanding of factors that may place individuals at risk for persistent APSP.

3.2.3 Study design

This study leveraged an existing Enhanced Recovery After Surgery (ERAS) dataset (Kehlet & Joshi, 2017; Althans et al., 2023), combined with medical record review to understand acute post-surgical pain (APSP) trajectories and associated factors in adult patients (>18 years) diagnosed with gynecologic cancer and who underwent abdominal hysterectomy.

3.2.3.1 Setting and sample

This study was conducted with the approval of the University of Pittsburgh's Office of Human Subjects Research Protection (STUDY20050087). Data extraction focused on patients in the UPMC ERAS dataset who underwent hysterectomy from January 1st, 2019, to December 31st,

2021. Inclusion criteria included adults (>18 years) with suspected gynecologic cancer who underwent abdominal hysterectomy performed by gynecologic oncology surgeons. Individuals who were subsequently found to have benign conditions were excluded from analyses.

3.2.3.2 Measures and Data collection

The data includes a combination of medical record and ERAS data. See **Table 3-1** for variables, source, and operationalization.

Table 3-1 Variables and operationalization from medical records and ERAS dataset

Variables	Source	Operationalization
Dependent variable		
Acute pain	ERAS dataset	Mean pain severity (0 = no pain; 10 = most pain possible) for immediate post-op period and each of post-op days 1-5
Demographic and lifestyle factors (independent variables)		
Age	ERAS dataset	Age at surgery from ERAS dataset
Race	ERAS dataset	Race was categorized into white, black, Asian, not specific or declined
Marital status	Medical records	Classified into 1-Partnered (includes married and living with partner,); 2-Nonpartnered. (includes single, married, divorced, and widowed).
Smoking	Medical records	1 – Never smoker; 2 – Former smoker; 3 – Current smoker (Data extraction instructions: Go to the last clinical visit before surgery and check the smoking questions: Do you currently smoke? Have you ever smoked in the past)
Alcohol use	Medical records	1-Yes; 0-No; (Data extraction instructions: Go to the last clinical visit before surgery and check the alcohol use questions: Do you drink alcohol (alcohol use Yes or No)
BMI	ERAS dataset	BMI at surgery from ERAS dataset.

Medical history factors		
Diagnosis	Medical records	Cancer diagnosis was categorized into: 1-Endometrial cancer; 2-Ovarian/ Fallopian tubal/Peritoneal cancer; 3-Cervical cancer. Identified from pathology report associated with the index surgery.
Cancer stage	Medical records	FIGO stage (1-I; 2-II; 3-III; 4-IV), identified from pathology report associated with the index surgery.
Charlson Comorbidity Index (CCI) scores	ERAS dataset	CCI is derived by summing the assigned weights of all diagnosed comorbid conditions. Higher scores indicate a more severe set of diagnoses. (Charlson, Szatrowski, Peterson, & Gold, 1994)
Previous pelvic or abdominal surgery including Cesarean section, Laparotomy, and Laparoscopy	Medical records	0-No; 1-Yes; confirm previous surgery occurred prior to date of index surgery.
Anxiety diagnosis	Medical records	1-Yes; 0-No (found from Epic problem list and confirmed date of diagnosis was prior to index surgery)
Depression diagnosis	Medical records	1-Yes; 0-No before index surgery (found from Epic problem list and compare date of diagnosis and surgery)
Perioperative factors		
Operation date	ERAS dataset	Record date
Surgery procedure	ERAS dataset	The surgery procedure includes Laparoscopic Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy (BSO), Robotic-Assisted Abdominal Hysterectomy, Laparoscopic Abdominal Hysterectomy, Robotic-Assisted Abdominal Hysterectomy, Total Abdominal Hysterectomy, Total Abdominal Hysterectomy with BSO. The study recategorized them into 1-minimal invasive hysterectomy; 2- Total abdominal hysterectomy
American Society of Anesthesiologists	ERAS dataset	ASA class was assessed by the anethesiologist before index surgery with

Classification (ASA Class)		the following classes: ASA I -A normal healthy patient; ASA II-A patient with mild systemic disease without significant functional limitation; ASA III-A patient with severe systemic disease with significant functional limitation; ASA IV-A patient with severe systemic disease with constant threat to life. The study categorized the ASA class into ASA<=2 and ASA>=3.
Surgery procedure time	ERAS dataset	Total minutes in surgery
Preoperative pelvic pain	Medical records	1-Yes; 0-No before surgery (found from the last clinical visit before the date of index surgery)
Preoperative opioid use	ERAS dataset	1-Yes; 0-No before index surgery

3.2.3.3 Data analysis

All analyses were conducted using SPSS version 27 (IBM Corp, Armonk, NY) and SAS version 9.4 (SAS Institute, Cary, NC). Mean and standard deviation (SD) for numerical data and frequency (percentage) for categorical data were calculated. The SAS PROC TRAJ procedure(JONES et al., 2001) were used to conduct the group-based trajectory modeling to examine the patterns of acute pain from post-hysterectomy day 0 to day 5.

Group-based trajectory modeling is a statistical approach that identifies groups of patients with similar changes in a particular variable over time, without assuming the existence of a specific trend or number of groups(Nagin & Odgers, 2010). This method requires at least 100 participants (ideally more than 300) and a minimum of 3 time points. In this study, group-based trajectory modeling quantifies both initial pain intensity and rate of pain resolution. Model complexity and overall fit is evaluated based on the Bayesian information criterion (BIC). A smaller BIC indicates a better fit. The SAS PROC TRAJ procedure also provides probabilities that an individual belongs

to each of the modeled trajectory groups. Average probability (AvePP) for members of a trajectory group should be $\geqslant$0.70(Daniel S. Nagin, 2010). Selection of the best trajectory model was based on multiple criteria: low values for BIC, high AvePPs for members of a trajectory group, a minimum trajectory class size of 5% of total study population, and parsimony(Ram & Grimm, 2009).

Univariate Pearson chi-squared and one-way ANOVA were then used to compare the demographic and lifestyle factors, medical history (including psychological) factors, and perioperative characteristics among identified acute pain trajectory groups. The purpose of this step was to identify the unadjusted effects of the predictor variables on trajectory group membership to select variables to be included in the multivariate model. Variables with a statistical probability (p) value below 0.30 were included in the multiple multinomial logistic regression risk analysis. We then calculated the Variance Inflation Factor (VIF) to assess multicollinearity(P. Vatcheva & Lee, 2016). For continuous variables, the VIF was computed by regressing each variable against every other variable in the model. For category variables, dummy codes were created to compute VIFs for dummy variables. A VIF value of 1 indicates no multicollinearity. Generally, a VIF between 1 and 5 is considered acceptable(P. Vatcheva & Lee, 2016).

In the multiple multinominal regression model, the last pain trajectory group was designated as the reference category. We also identified variables with rare cases in specific groups, which can lead to unstable estimates with extremely high odds ratios or wide confidence intervals. Bonferroni corrected p values of the affected risk factors were obtained and $p < 0.05$ was considered statistically significant.

3.2.4 Results

3.2.4.1 Patient Characteristics

The ERAS dataset screening identified 2354 patients who underwent a hysterectomy by a gynecologic oncologist, of which 1323 had a confirmed gynecologic cancer diagnosis and were eligible for inclusion. See Table 2 for descriptive statistics for all variables. The average age of patients was 64.10 years (SD=10.58), with mean BMI of 35.47 (SD=15.19), and the majority identified as non-Hispanic white (92.4%). Most patients underwent laparoscopic hysterectomy (56.2%), were diagnosed with endometrial cancer (81.4%), and had an ASA class of >=3 (62.5%). A majority never smoked (66.5%), didn't consume alcohol (61.0%), and had no history of cesarean section (84.5%), previous laparotomy (72.5%), or laparoscopy (56.3%). Among patients, 24.8% had previously been diagnosed with anxiety, 19.9% with depression, and 30.8% reported experiencing preoperative pelvic pain.

Table 3-2 Descriptive statistics(N=1323)

	Frequency (Percent%)	Mean (SD)
Age		64.10 (10.58)
BMI		35.47 (15.19)
CCI Scores		1.93 (1.27)
Surgery procedure time (in minutes)		143.15 (68.34)
Post hysterectomy length of stay in hospital		1.67 (2.94)
Marital Status		
Partnered	737 (55.7)	
Non-partnered	584 (44.1)	
Missing	2 (0.2)	
Race		
White	1224 (92.4)	
Black	61 (4.6)	
Asian	4 (0.3)	
Not specific or declined	34 (2.6)	
Diagnosis		

Endometrial cancer	1077 (81.4)	
Ovarian/ Fallopian tubal/Peritoneal cancer	235 (17.8)	
Cervical cancer	11 (0.8)	
Alcohol consumption		
Yes	490 (37.0)	
No	807 (61.0)	
Missing	26 (2.0)	
Smoking		
Never smoker	881 (66.5)	
Former Smoker	315 (23.8)	
Current Smoker	100 (7.6)	
Missing	27 (2.0)	
Cancer stage		
I	838 (63.3)	
II	79 (6.0)	
III	323 (24.4)	
IV	83 (6.3)	
Cesarean section history		
Yes	190 (14.4)	
No	1119 (84.5)	
Missing	14 (1.1)	
Laparotomy history		
Yes	176 (13.3)	
No	959 (72.5)	
Missing	188 (14.2)	
Laparoscopy history		
Yes	445 (33.6)	
No	713 (53.9)	
Missing	165 (12.5)	
Anxiety diagnosis		
Yes	328 (24.8)	
No	980 (74.1)	
Missing	15 (1.1)	
Depression diagnosis		
Yes	263 (19.9)	
No	1045 (79.0)	
Missing	15 (1.1)	
Preoperative pelvic pain		
Yes	408 (30.8)	
No	910 (68.8)	
Missing	5 (0.4)	
Preoperative opioid use		
Yes	499 (37.7)	
No	824 (62.3)	
Missing	0 (0)	

Surgery Procedure Minimal invasive hysterectomy Total abdominal hysterectomy	 1050 (79.3) 273 (20.6)	
ASA class <=2 >=3	 496 (37.4) 828 (62.5)	

3.2.4.2 Pain Trajectories

The process for selection of different trajectory shapes were presented in supplementary 1. The study identified 4 trajectory groups based on group-based trajectory modeling. **Manuscript-2 Figure 1** showed the four trajectory groups.

No pain group

Ten percent of patients(N=141) experienced an average level of no pain throughout the first 5 days post-hysterectomy.

Rapid resolution group

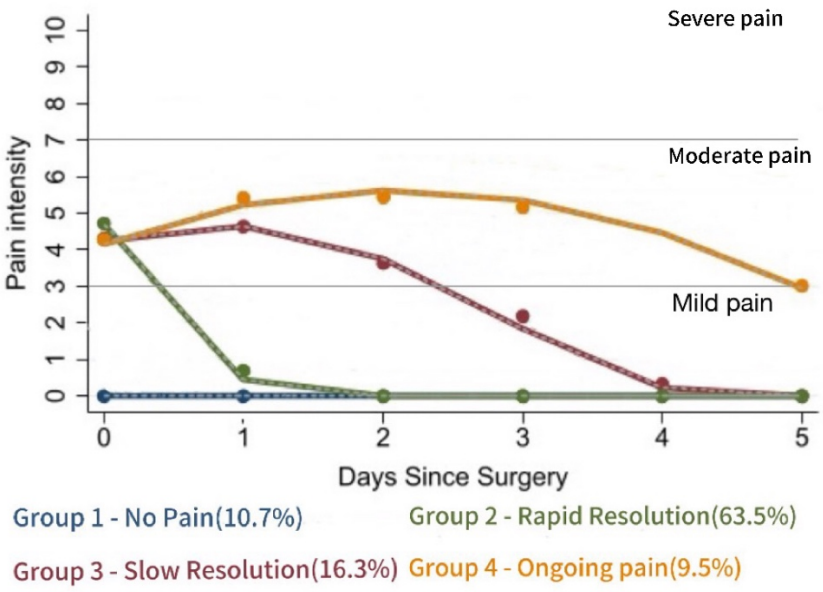
Sixty three percent of patients (N=840) reported moderate pain level on the day of hysterectomy and their pain rapidly diminished the first post-op day. Through the 2nd to 5th post-op day, they remained pain free.

Slow resolution group

Sixteen percent of patients (N=216) experienced moderate pain levels through the first post-op day and their pain level gradually decreased each day. By the 4th day post hysterectomy, patients in this group reported no pain.

Ongoing pain group

Nine percent of patients (N=126) in this trajectory group reported moderate pain levels on the day of hysterectomy and their pain intensity slightly increased from the first to the third day post-hysterectomy and then started decreasing. Patients still experienced mild pain on post-op day 5.



6 Manuscript 2 Figure 1 APSP trajectory groups for patients with gynecological cancer

3.2.4.3 Predictors of Acute Pain Trajectory Membership

The sociodemographic and lifestyle, medical history, and perioperative characteristics were compared among trajectory groups. BMI, CCI scores, surgery procedure time, diagnosis, smoking, cancer stage, laparotomy history, laparoscopic history, anxiety diagnosis, preoperative pelvic pain**,** surgery procedure, and ASA class were included in the multinomial logistic regression model ($p < 0.30$ in univariate analyses; See **Table 3-3**).

BMI, CCI scores, surgery procedure time, diagnosis, smoking, cancer stage, laparotomy history, laparoscopic history, anxiety diagnosis, preoperative pelvic pain, preoperative opioid use, surgery procedure, and ASA class were examined by VIF scores to ensure no multicollinearity before multinomial logistic regression analysis. None of these baseline characteristics violated multicollinearity (S2). The results of multiple multinomial logistic regression analysis are reported in **Table 3-4**.

The McFadden Pseudo R^2 for the multinominal regression model was 0.420 ($p<0.001$). Four predictors (anxiety diagnosis, preoperative pelvic pain, surgery procedure and ASA class) were significant for ALL groups comparisons. CCI Scores, preoperative opioid use, and surgery procedure time (in minutes) were significant predictors for being in the no pain or quick resolution trajectories vs the ongoing pain trajectory group. Specifically, for every one unit increase in the CCI score (indicating more severe comorbidities), the odds of being in the 'no pain' trajectory group decreased by 28% and the odds of being in the 'rapid resolution' trajectory group decreased by 24% compared to the 'ongoing pain' trajectory group. For every one-minute increase in surgery procedure time, the odds of being in the 'no pain' and ‘rapid resolution’ trajectory groups decreased by 2% compared to the 'ongoing pain' group. Patients not using opioids preoperatively had 2.10 times higher odds of experiencing no pain (95% CI: 1.06-4.17, p=0.03) and 4.71 times higher odds of a quick pain resolution (95% CI: 2.84-8.73, p<0.01) compared with patients in ongoing pain group.Patients without diagnosis anxiety before the index surgery were more likely to be in the 'no pain' (OR=11.8), 'rapid resolution' (OR=12.7), or 'slow resolution' (OR=6.7) trajectory groups compared to those in the 'ongoing pain' trajectory group. Finally, patients who did not have preoperative pelvic pain had higher odds of being in the 'no pain' (OR=2.6), 'rapid resolution'(OR = 2.6), or 'slow resolution'(OR = 4.1) trajectory groups compared to those in the 'ongoing pain' trajectory group. Compared with total abdominal hysterectomy, patients undergoing minimally invasive hysterectomy had higher odds (ranging from 1.5 to 11.8) of being in the 'no pain', 'rapid resolution' and ‘slow resolution’ trajectory groups. Finally, patients with an ASA class of <=2 (indicating no functional limitation) are about 3 to 6 times of odds being in the 'no pain', 'rapid resolution', or 'slow resolution' groups than in the ongoing pain group compared to those with an ASA class of >=3 (indicating significant functional limitation).

Table 3-3 Univariate analysis

Mean (SD)/N (%)	Group 1 (N=141)	Group 2 (N=840)	Group 3 (N=216)	Group 4 (N=126)	F/X^2	P value
Age	64.26(10.2)	64.13(10.6)	63.68(10.8)	64.47(10.7)	0.18	0.912
BMI	34.97(9.9)	36.55(13.9)	34.39(23.3)	30.64(8.0)	6.10	<0.001**
CCI Scores	1.81(1.1)	1.99(1.2)	1.83(1.6)	1.87(1.6)	1.50	0.21*
Surgery procedure time (in minutes)	131.76(40.1)	125.23(36.1)	178.47(113.1)	214.84(84.9)	106.62	<0.001**
Marital Status						
Non-Partnered	56(39.7)	366(43.7)	104(48.1)	58(46.0)		
Partnered	85(60.3)	472(56.3)	112(51.9)	68(54.0)	2.78	0.427
Race#						
White	127(90.1)	786(93.6)	197(91.2)	114(90.5)		
Black	5(3.5)	34(4.0)	14(6.5)	8(6.3)		
Asian	1(0.7)	2(0.2)	0(0)	1(0.8)		
Not specific or declined	8(5.7)	18(2.1)	5(2.3)	3(2.4)	12.18	0.21#
Diagnosis¥						
Endometrial cancer	128(90.7)	796(94.8)	103(47.7)	50(39.7)		
Ovarian/ Fallopian tubal/Peritoneal cancer	12(8.6)	36(4.3)	111(51.4)	76(60.3)	436.50	<0.001**
Cervical cancer	1(0.7)	8(0.9)	2(0.9)	0(0)		
Alcohol consumption						
Yes	57(40.7)	310(37.5)	72(34.6)	51(41.8)	2.27	0.518
No	83(59.3)	517(62.5)	136(65.4)	71(58.2)		
Smoking						
Never smoker	101(72.1)	573(69.5)	131(62.7)	76(62.3)		
Former Smoker	28(20.0)	195(23.6)	59(28.2)	33(27.0)		
Current Smoker	11(7.9)	57(6.9)	19(9.1)	13(10.7)	7.57	0.272*
Cancer stage						
I	99(70.2)	557(66.3)	133(61.6)	49(38.9)		
II	8(5.7)	42(5.0)	16(7.4)	13(10.3)		
III	26(18.4)	201(23.9)	49(22.7)	47(37.3)		
IV	8(5.7)	40(4.8)	18(8.3)	17(13.5)	46.34	<0.001**
Cesarean section history						
Yes	24(17.3)	124(14.8)	27(12.8)	15(12.4)		
No	115(82.7)	714(85.2)	184(87.2)	106(87.6)	1.84	0.606
Laparotomy history						
Yes	17(13.7)	103(14.4)	33(17.8)	23(20.5)	3.87	0.276*
No	107(86.3)	611(85.6)	152(82.2)	89(79.5)		
Laparoscopy history						
Yes	44(35.5)	301(41.1)	64(34.0)	36(31.9)	6.20	0.102*
No	80(64.5)	432(58.9)	124(66.0)	77(68.1)		
Anxiety diagnosis						

Yes No	28(29.3) 110(79.7)	185(22.1) 652(77.9)	46(21.7) 166(78.3)	69(50.7) 52(43.0)	72.64	<0.001**
Depression diagnosis Yes No	25(18.1) 113(81.9)	162(19.4) 675(80.6)	46(21.7) 166(78.3)	30(24.8) 91(75.2)	2.62	0.453
Preoperative pelvic pain Yes No	39(27.7) 102(72.3)	205(24.4) 634(75.6)	76(35.5) 138(64.5)	88(70.1) 36(29.0)	112.38	<0.001**
Preoperative opioid use Yes No	52 (36.9) 89 (63.1)	251 (29.9) 589 (70.1)	117 (54.2) 99 (45.8)	79 (62.7) 47 (37.3)	80.35	<0.001**
Surgery Procedure Minimal invasive hysterectomy Total abdominal hysterectomy	134(95%) 7(5.0)	835(99.4%) 5(0.6)	67(31.0) 149(69.0)	14(11.1) 112(88.9)	893.83	<0.001**
ASA class <=2 >=3	67(47.5) 74(52.5)	334(39.8) 506(60.2)	71(32.9) 145(67.1)	23(18.3) 103(81.7)	29.78	<0.001**

The study conducted a sensitivity test for race. After excluding the few instances of Asian and Not Specific or Declined, the chi-square test yielded the differences between white and black with $X^2(3) = 3.47$, $p = 0.325$.

Ɏ The study conducted a sensitivity test for diagnosis. After excluding the few instances of cervical cancer, the chi-square test yielded the difference between endometrial cancer and ovarian/ fallopian tubal/peritoneal cancer with $X^2(3) = 434.24$, $p < 0.001$.

*$p < 0.30$, multiple multinomial logistic regression parameters

**$p < 0.05$

Table 3-4 Odd ratios when comparing each of the following trajectory groups to the ongoing pain trajectory group: A. no pain trajectory, B. quick resolution trajectory, and C. slow resolution trajectory

Variables	A. No pain vs. Ongoing pain			B. Quick resolution vs. Ongoing pain			C. Slow resolution vs Ongoing pain		
	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p
BMI	1.02	0.96-1.04	0.99	1.03	0.99-1.08	0.09	1.04	1.01-1.08	0.03
CCI Scores	**0.72**	**0.49-0.90**	**0.03**	**0.76**	**0.58-0.99**	**0.04**	0.92	0.74-1.13	0.40
Surgery procedure time (in minutes)	**0.98**	**0.97-0.99**	**0.01**	**0.98**	**0.97-0.99**	**0.01**	0.99	0.99-1.01	0.31
Diagnosis[#]									

Endometrial cancer vs Ovarian/ Fallopian tubal/Peritoneal cancer(ref)	1.75	0.54-5.62	0.35	2.80	1.01-7.82	0.06	0.75	0.37-1.50	0.40
Smoking Never smoker vs Current Smoker	1.35	0.35-5.23	0.66	2.12	0.63-7.17	0.23	1.30	0.47-3.64	0.61
Former Smoker vs Current Smoker	0.61	0.14-2.67	0.51	1.19	0.32-4.44	0.79	1.29	0.42-3.95	0.66
Cancer stage I vs IV	1.89	0.41-8.84	0.42	1.83	0.46-7.22	0.39	1.73	0.62-4.82	0.30
II vs IV	0.85	0.11-6.75	0.88	1.01	0.16-6.54	0.99	0.81	0.21-3.08	0.75
III vs IV	0.89	0.11-3.05	0.53	0.92	0.22-3.90	0.91	0.87	0.29-2.55	0.80
Laparotomy history No vs Yes(ref)	2.11	0.71-6.31	0.18	2.07	0.80-5.38	0.13	1.59	0.74-3.42	0.24
Laparoscopy history No vs Yes(ref)	0.64	0.27-1.52	0.32	0.55	0.25-1.24	0.15	0.90	0.45-1.78	0.75
Anxiety diagnosis No vs Yes(ref)	**11.81**	**4.63-30.11**	**0.01**	**12.67**	**5.46-29.38**	**0.01**	**6.68**	**3.40-13.11**	**0.01**
Preoperative pelvic pain No vs Yes(ref)	**2.64**	**1.10-6.34**	**0.02**	**2.57**	**1.16-5.71**	**0.02**	**4.14**	**2.21-7.76**	**0.02**
Preoperative opioid use No vs Yes(ref)	**2.10**	**1.06-4.17**	**0.03**	**4.71**	**2.84-8.73**	**0.01**	1.68	0.92-3.04	0.09
Surgery Procedure[¥] minimal invasive hysterectomy laparoscopic vs Total abdominal hysterectomy	**264.18**	**61.50-1134.00**	**0.01**	**4.03**	**1.56-10.40**	**0.01**	**140.48**	**79.25-257.65**	**0.01**
ASA class <=2 VS >=3(ref)	**6.21**	**2.45-16.11**	**0.01**	**4.88**	**1.98-12.03**	**0.01**	**3.10**	**1.50-6.44**	**0.01**

The McFadden Pseudo R square for the overall model is 0.420, $p<0.001$.

[#] Since the cases of cervical cancer were rare and there were no cases of cervical cancer in the ongoing pain group, the multinomial regression analysis excluded cases with cervical cancer. The analysis then compared endometrial cancer to ovarian/fallopian tubal/peritoneal cancer.

[Ɣ] Due to the rare cases in the cross table of surgery procedures and pain trajectory groups, which could lead to unstable estimates, the table displays the 95% CI determined after 1,000 bootstrap iterations specifically for the surgery procedure variable.

3.2.5 Discussion

The primary aim of the study was to identify and characterize distinct acute pain trajectories among patients with gynecologic cancer who underwent hysterectomy and to identify factors associated with membership in these distinct trajectories. Patients' socio-demographic and lifestyle characteristics, medical history, and perioperative factors were compared across the different acute pain trajectories. To the best of our knowledge, this is the first study to comprehensively explore acute pain trajectories among patients undergoing hysterectomy for gynecologic cancers.

3.2.5.1 Acute Pain Trajectories

Group based trajectory modeling identified 4 distinct patterns of acute pain from day of surgery to 5 days post hysterectomy: no pain, rapid pain resolution, slow pain resolution, and ongoing pain. While all most trajectory groups (rapid resolution, slow resolution and ongoing pain) reported moderate pain intensity immediately after hysterectomy (4-5 on a 0-10 scale), distinct trajectories of pain resolution emerged on post hysterectomy day 1. Approximately 10% experienced a trajectory characterized by an absence of pain throughout the initial 5 postoperative days. A

majority (63%) followed a rapid resolution trajectory, reporting moderate pain levels on the surgery day that rapidly diminished. The fact that more than 70% of patients were in the no pain and rapid pain resolution groups highlights the efficacy of early pain management after abdominal hysterectomy. In contrast, 16% exhibited a slow resolution trajectory, with gradual pain reduction. And approximately 9% had an ongoing pain trajectory, experiencing persistent mild pain 5 days post-hysterectomy. The slow resolution and ongoing pain trajectories highlight the complexity of postoperative pain experiences and the need for sustained pain management strategies beyond the immediate recovery period. Overall, these trajectories shed light on the dynamic nature of postoperative pain, and emphasize the importance of early, tailored pain management interventions and ongoing support to optimize recovery after surgery for gynecologic cancer.

3.2.5.2 Risk factors associated with membership in the different pain trajectories

Our study uncovered several critical factors influencing membership in the distinct APSP trajectories.

Psychological Risk Factors Anxiety has often been observed to coexist with pain and may amplify postoperative pain trajectories (Wang et al., 2018). In our analysis, a pre-surgery anxiety diagnosis was a potent risk factor for sustained post-operative pain, while depression was not a significant predictor. Notably, anxiety is a distinguishing factor for patients in the unfavorable groups: 'slow resolution' and 'ongoing pain' trajectories. This suggests that interventions targeting anxiety might significantly alter the development trajectory of ongoing pain.

Medical History Factors: Patients with better preoperative physical status, as indicated by the lower ASA class, lower CCI scores, and the absence of preoperative pelvic pain status, were less

likely to experience ongoing pain after hysterectomy. These findings align with previous research about complications of hysterectomy. For example, study found that analgesic purchase after hysterectomy was independently predicted by ASA class(Daugbjerg et al., 2014) and patients of higher ASA class recovered less well compared with patients of lower ASA class (Theunissen et al., 2016).

Perioperative factors: Preoperative pelvic pain is another significant factor differing ongoing pain and other trajectory groups. This suggests the possibility that there might be underlying pathologies or sensitization processes affecting pain experience. Chronic preoperative pelvic pain may alter pain thresholds and pain perception, leading to a reduced ability to tolerate new pain stimuli. Previous studies have also identified the significance of preoperative pelvic pain. For example, a study of postoperative pain in 214 women after laparoscopic hysterectomy found that those with pre-existing chronic pelvic pain experienced heightened post-surgical pain(Kanellos et al., 2021). However, existing literature has predominantly focused on benign conditions(Kanellos et al., 2021; Osler et al., 2011; Theunissen et al., 2017). Our exploration of risk factors differentiating between acute pain trajectories has underscored the importance of presurgical physical status such as ASA class, CCI scores, and preoperative pain in understanding post-operative pain among patients with gynecologic cancer. Regarding opioid use, patients who did not use opioids before surgery were more likely to experience no pain or quicker pain resolution post-hysterectomy. This emphasizes the need to consider preoperative opioid usage patterns when evaluating post-surgical pain outcomes.

The study findings also highlight the significance of surgical procedure time and procedure type in influencing pain trajectories, with longer durations and total abdominal hysterectomies correlating with an increased risk for persistent post-hysterectomy pain. This association can be

attributed to the pronounced tissue trauma and extensive surgical manipulation inherent in such procedures, emphasizing the importance of considering surgical factors in tailoring pain management strategies for improved patient outcomes.

Sociodemographic/lifestyle factors: None of the sociodemographic or lifestyle factors were found to be significant in predicting APSP trajectories.

3.2.5.3 Implications for nursing

The presence of these four acute pain trajectories advances our understanding of acute post-hysterectomy pain among patients with gynecologic cancer. Future research should delve deeper into the long-term consequences and implications of these pain trajectories, such as post-operative complications, the development of chronic postoperative pain, or opioid use. The study also highlights that preoperative physical status (CCI scores, ASA class), preoperative pelvic pain, surgical procedure and duration, and preoperative anxiety significantly influence pain trajectory memberships. Identifying these risk factors for ongoing pain can aid in tailoring pain management strategies to address the unique needs of these patients. Future research could delve into the mechanisms through which these factors impact pain experiences.

The study's findings hold significant implications for clinical practice. The risk factors for ongoing pain can be instrumental in helping healthcare providers identify patients who may benefit from more personalized pain management strategies. A comprehensive preoperative assessment, especially focusing on patients with a history of chronic pelvic pain and their psychological well-being, is crucial especially for patients with cancer, who may have intensive treatment and more psychological burden. In terms of tailored pain management to meet the complex need of cancer patients, although patient-controlled analgesia (PCA) pumps have traditionally been the standard

for postoperative pain management, recent research advocates for a multimodal approach. The approach combines standard narcotics with nonnarcotic options like anti-inflammatory agents, nerve blocks, N-methyl-D-aspartate antagonists such as dextromethorphan, magnesium, gabapentin, and acetaminophen(Azari et al., 2013). Notably, even patients with higher ASA class, indicating a greater health burden, have shown potential benefits from multimodal pain management approaches, with some experiencing earlier discharges compared to those managed conventionally(Santoso et al., 2014).

Limitations

We note the following limitations. First, the generalizability of our findings may be limited due to the predominant representation of white patients with endometrial cancer in our sample. However, generalizability is increased due to our large sample size. Second, our data source primarily relied on retrospective information obtained from medical records and the Enhanced Recovery After Surgery (ERAS) dataset, which did not allow for a comprehensive assessment of socioeconomic status and other psychological factors such as pain catastrophizing and fear of surgery. In addition, certain parameters, such as anxiety and preoperative pain, were not assessed using more objective or detailed methods. Considering the time and resources necessary to collect this information in a prospective manner, our retrospective study represents an efficient, large sample study to explore post-operative pain trajectories.

In conclusion, this study has provided valuable insights into acute pain trajectories following abdominal hysterectomy in patients with gynecologic cancer. We identified four distinct trajectories, ranging from no pain to ongoing pain, emphasizing the dynamic nature of postoperative pain experiences. The study highlights the significance of preoperative factors such

as ASA class, CCI scores, preoperative pelvic pain, surgical procedure (and duration), and preoperative anxiety in influencing these trajectories. These risk factors can aid healthcare providers in tailoring pain management strategies to meet the unique needs of individual patients. Future research should explore the long-term consequences of these pain trajectories and delve into the underlying mechanisms to further optimize pain management strategies for gynecologic cancer patients undergoing abdominal hysterectomy.

3.2.6 Supplementary materials

Appendix C show all the supplementary materials for manuscript#2 including the process for selection of different trajectory shapes (e.g., linear, quadratic, cubic) and Variance Inflation Factor (VIF) Among Baseline Factors. By comparing different trajectory shapes based on their BIC values, we chose three specific shapes with the smallest BICs. Then the study further assessed the AvePP value of the three specific shapes and ultimately the trajectory shape labeled as (1 2 2 2) was chosen. Mean fit estimates for the selected model of 4 trajectory groups were excellent: 0.89 for no pain group, 0.95 for rapid resolution group, 0.98 for slow resolution group and 0.97 for ongoing pain group.

3.3 DISSERTATION MANUSCRIPT 3: LONG TERM OUTCOMES OF APSP

Acute Pain Trajectories for Abdominal Hysterectomy in High-Risk Gynecological Cancer Patients: Implications for Length of Hospital Stay, Persistent Postsurgical Pain, and Prolonged Opioid Use

3.3.1 Abstract

Background: The evolution of acute postoperative surgical pain (APSP) into chronic pain and the potential for increased opioid-related complications post-hysterectomy in patients with gynecological cancer remains poorly understood. This study aimed to delineate distinct APSP trajectories and evaluate their associations with longer-term postoperative outcomes.

Methods: Utilizing an existing Enhanced Recovery After Surgery (ERAS) dataset combined with medical record reviews, this ancillary study assessed APSP trajectories over five days following hysterectomy in adult patients diagnosed with gynecological cancer. Group based trajectory modeling approach was used to identify APSP trajectories and generalized linear models were used to find out the associations between APSP trajectory memberships and post discharge outcomes including persistent postsurgical pain, thirty-day readmission, and prolonged opioid use.

Results: In total, 407 patients were analyzed and categorized into three distinct pain trajectory groups: quick resolution (T1), slow resolution (T2), and ongoing pain (T3). Significant differences in persistent pain, 30-day readmission rates, and prolonged opioid use were observed among the three trajectory groups. The quick resolution group (T1) exhibited significantly lower persistent pain at 2 weeks ($b = -0.99$, $p = 0.02$) and 2 months ($b = -0.84$, $p = 0.02$) compared to the ongoing

pain group (T3). Both T1 and T2 groups were less likely to be readmitted within 30 days than T3 (T1: b = -1.06, p = 0.04; T2: b = -1.97, p = 0.01). No significant differences in prolonged opioid use at 2 weeks and 2 months were found based on trajectory group.

Conclusions: The study identified distinct acute pain trajectories post-hysterectomy and demonstrated their significant associations with persistent pain and 30-day readmission. These findings highlight the potential of APSP trajectories to serve as early indicators for poor postoperative outcomes, enabling healthcare providers to pinpoint patients who may benefit from targeted preventive interventions. Future research should aim to elucidate the underlying mechanisms driving these associations and to develop tailored management strategies for high-risk patients.

Keywords: Acute pain trajectories, Hysterectomy, Gynecological cancer, Postoperative outcomes, Persistent pain, Opioid use.

3.3.2 Introduction

Gynecological cancer remains a significant health concern worldwide. Particularly alarming are high-risk gynecological cancers like ovarian cancer and high-grade endometrial cancer, which often require aggressive surgeries followed by chemotherapy and other adjuvant therapies. Hysterectomy stands as a pivotal treatment for these malignancies, while after this procedure, most patients experience acute postsurgical pain (APSP) which generally resolves within 1 weeks. This APSP is a psychophysiological response initiated by the activation of high-threshold nociceptors, often categorized by acute trauma (somatic or incision pain) or by damage to internal organs (visceral pain) due to surgical interventions (Brandsborg, 2012).

The evolution of acute postsurgical pain is dynamic and multifaceted, influenced by factors such as tissue damage, perioperative medicine interactions, and unique patient characteristics. Even though monitoring of APSP in the clinic is dynamic and timely, research often uses methods like singular postoperative day measurements or two-day average scores to represent APSP. These methods seldom fully reflect the dynamic nature of APSP. Group-based trajectory modeling (GBTM) offers an innovative analytical approach, enabling categorization of patients into distinctive pain trajectory clusters, such as pain resolution over time, consistent pain, or escalating pain intensity (Chapman et al., 2012). Going beyond single-time pain intensity, evaluating acute pain trajectories could illuminate this phenomenon further, capturing both pain intensity and its evolution across multiple postoperative days. Recent studies in other medical contexts have supported this notion (Okamoto et al., 2018), but such studies remain unexplored post-hysterectomy in high-risk gynecological cancer patients.

Acute postoperative pain can not only extend a patient's hospital stay, increasing medical expenses, but also correlates with severe postoperative complications like cardiovascular and thrombosis-related diseases (Gan, 2017). Importantly, if unmanaged, the acute pain experienced during hysterectomy can develop into a chronic affliction, significantly impacting health. Studies highlight this, with 10%-50% of patients reporting acute postoperative pain after hysterectomy transitioning into chronic postsurgical pain (Theunissen et al., 2016; Brandsborg et al., 2009; Katz & Seltzer, 2009). Moreover, unresolved APSP could lead to an increase in opioid use postoperatively. While opioids can be effective in alleviating intense pain in the immediate post-surgical phase, their prolonged use poses significant risks such as opioid dependence and addiction. When opioid use extends into adjuvant chemotherapy, it can significantly compromise the overall well-being of patients and adversely affect treatment outcomes(Darnall et al., 2012).

This is due to heightened risks like exacerbated gastrointestinal issues, increased susceptibility to infections from a weakened immune system, and the compounding effects of cognitive impairments and mood disorders(Scarborough & Smith, 2018).

Despite growing insights into the fact that the APSP that can evolve into a chronic pain and the increased risk of opioid-related complications, a comprehensive understanding of its trajectory post-hysterectomy remains incomplete. Previous studies have established some understanding of the long-term effects of APSP. However, the dynamic trajectory of APSP and its long-term implications after hysterectomy still warrant further exploration.

The objectives of the study are to 1) explore distinct post-operative acute pain trajectories over 5 days following hysterectomy in patients with high-risk gynecological cancer; 2) assess the associations between acute pain trajectories and outcomes including 30-day readmission, prolonged post-surgical pain, and prolonged opioid use. This research seeks to advance our understanding of acute pain trajectories and outcomes in high-risk gynecological cancer patients to improve personalized patient recovery and well-being.

3.3.3 Methods

3.3.3.1 Study design

This ancillary study uses an existing Enhanced Recovery After Surgery (ERAS) dataset combined with medical records review to understand acute post-surgical pain (APSP) trajectories and outcomes in adult patients (>18 years) diagnosed with gynecological cancer who underwent an abdominal hysterectomy and also received chemotherapy.

3.3.3.2 Setting and sample

This study was conducted with the approval of the University of Pittsburgh's Ethical Review Board (STUDY20050087). The ERAS dataset, established to improve surgical outcomes and recovery rates (Kehlet & Joshi, 2017), comprises patients from January 1st, 2019 to December 31st, 2021. (Althans et al., 2023). Data extraction focused on adult patients (>18 years) in the UPMC ERAS dataset who were found to be at high risk for recurrence. We defined this as patients who 1) underwent abdominal hysterectomy performed by gynecologic oncologists between January 1st, 2019, to December 31st, 2021, and 2) started adjuvant chemotherapy or continued their neoadjuvant chemotherapy within 2 months after surgery.

3.3.3.3 Measures

Independent Variable: Acute Pain Trajectory membership (see data analysis)

Outcomes:

Acute Pain: Sourced from the ERAS dataset, acute pain was assessed through a daily mean pain intensity over the first five post-operative days. Pain intensity measured on a numerical scale of 0-10, where 0 signifies no pain and 10 represents the maximum conceivable pain.

30-day readmission: Sourced from the ERAS dataset provides a binary (yes/no) indication of unplanned readmission within 30 days after hysterectomy.

Prolonged Post-Hysterectomy Pain: Extracted from medical records, this measure involved the routine pain assessment conducted during clinical visits at approximately 2-3 weeks post-surgery, utilizing a numerical pain scale ranging from 0 (no pain) to 10 (most intense pain).

Prolonged Opioid Use: Data from ERAS dataset and medical records provide a binary (yes/no) indication of opioid usage at two distinct post-hysterectomy intervals: 7 days post-surgery (from

ERAS dataset indicating Yes/No) and again at around 2 weeks and 2 months post-surgery (from medical records based on opioid refills>=1).

Covariates:

Clinical data such as age and BMI are collected from ERAS dataset and medical records (Medical history variables include diagnosis, anxiety diagnosis before the index surgery, neoadjuvant chemotherapy, presurgical opioid use and presurgical pain). Variables such as operation date, surgery procedure and anesthesia classification (ASA class) are gathered from the ERAS dataset.

3.3.3.4 Statistics

All analyses were conducted using SPSS version 27 (IBM Corp, Armonk, NY) and SAS version 9.4 (SAS Institute, Cary, NC). Mean and standard deviation (SD) for numerical data and frequency (percentage) for categorical data were calculated. The SAS PROC TRAJ procedure (JONES et al., 2001) were used to conduct the group-based trajectory modeling to examine the patterns of acute pain from post-hysterectomy day 0 to day 5.

Group-based trajectory modeling is a statistical approach that identifies groups of patients with similar changes in a particular variable over time, without assuming the existence of a specific trend or number of groups (Nagin & Odgers, 2010). This method requires at least 100 participants (ideally more than 300) and a minimum of 3 time points. It quantifies both initial pain intensity and rate of pain resolution. Model complexity and overall fit is determined on the Bayesian information criterion (BIC). A smaller BIC indicates a better fit. The SAS PROC TRAJ procedure also provides probabilities that an individual belongs to each of the modeled trajectory groups.

Average probability (AvePP) for members of a trajectory group should be ⩾0.70(Daniel S. Nagin, 2010).

ANOVA, chi-square tests were used accordingly to investigate significant differences for outcome variables between pain trajectory membership. Controlling for age, BMI, diagnosis, procedure, ASA class, anxiety diagnosis, neoadjuvant chemotherapy, preoperative opioid use and preoperative pelvic pain, generalized linear models were conducted to evaluate whether pain trajectory membership predicted length of stay, 30-day readmission, prolonged post-surgical pain, and prolonged opioid use.

3.3.4 Results

The study included 407 patients with high-risk gynecological cancer, having an average age of 63.35 years and a mean BMI of 34.15. Baseline characteristics for the sample are presented in **Table 3-5**.

Table 3-5 Descriptive statistics of baseline and outcome variables(N=407)

Characteristics	Frequency N (%)	Mean (SD)
Baseline		
Age		63.35 (10.73)
BMI		34.15 (17.79)
Diagnosis Endometrial cancer Ovarian/ Fallopian tubal/Peritoneal cancer	 247 (60.7) 160 (39.3)	
Cancer stage for endometrial cancer I II III IV	 61(24.7) 4(1.6) 157(63.6) 25(10.1)	
Cancer stage for Ovarian/ Fallopian tubal/Peritoneal cancer		

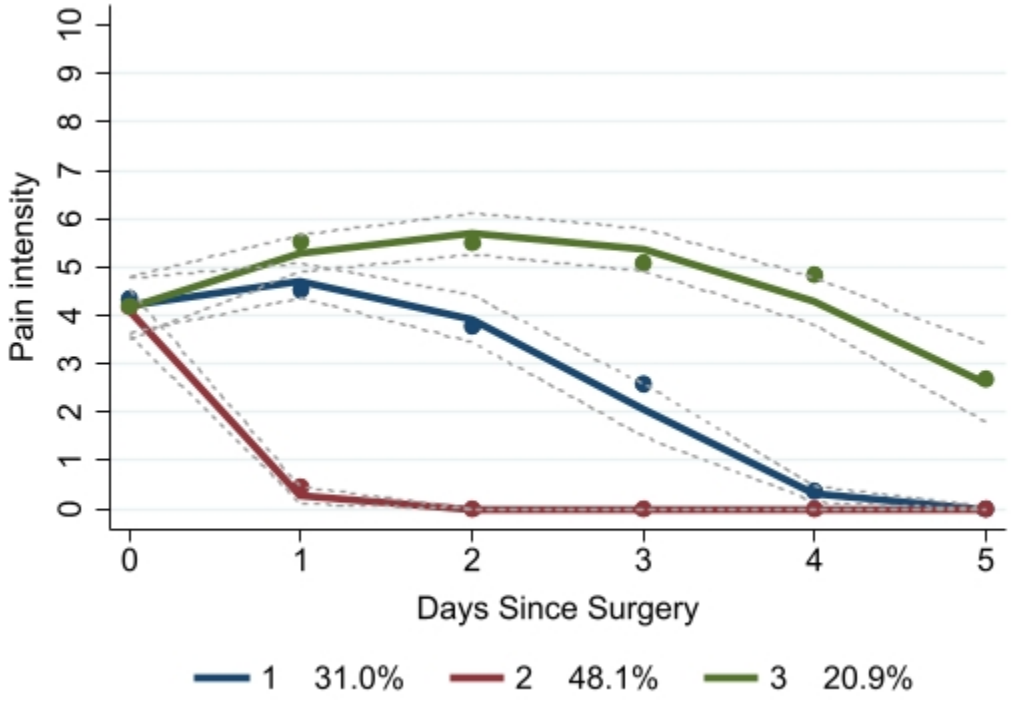
I II III IV	22(13.8) 8(5.0) 92(57.5) 38(23.8)	
Surgery procedure Minimally invasive surgery* Total abdominal hysterectomy	 220 (54.1) 187 (45.9)	
ASA class <=2 >=3	 137 (33.7) 270 (66.3)	
Preoperative pelvic pain Yes No Missing	 142 (34.9) 260 (63.9) 5 (1.2)	
Preoperative opioid use Yes No Missing	 156 (38.3) 251 (61.7) 0 (0)	
Anxiety diagnosis Yes No Missing	 100 (24.6) 300 (73.7) 7 (1.7)	
Neoadjuvant chemotherapy Yes No Missing	 40 (9.8) 367 (90.2) 0	
Outcomes		
Persistent post-hysterectomy pain at 2 weeks None Mild (1-3) Moderate to severe (>=4)	 272 (66.8) 75 (18.4) 60 (14.7)	
Persistent post-hysterectomy pain at 2 month (+/- one week) None Mild (1-3) Moderate to severe (>=4)	 306 (75.2) 66 (16.2) 35 (8.6)	
30-day readmission Yes No	 38 (9.3) 369 (90.7)	
Prolonged opioid use at 7 days after surgery Yes No	 17 (4.2) 390 (95.8)	
Prolonged opioid use at 2 weeks after surgery Yes No	 37 (9.1) 370 (90.9)	

Prolonged opioid use at 2 months after surgery		
Yes	21 (5.2)	
No	386 (94.8)	

* Minimally invasive surgery includes laparoscopic abdominal hysterectomy and robotic-assisted abdominal hysterectomy

3.3.4.1 Acute Pain trajectories

The process for selection of different trajectory shapes is presented in **Appendix D** under **Supplementary Tables 1**. The study identified 3 trajectory groups based on group-based trajectory modeling (**Manuscript 3 Figure 1**).



7 Manuscript 3 Figure 1APSP trajectory groups for patients with high-risk gynecological cancer

Quick Resolution Group:

Around 49.7% of the patients (N=196) from the study experienced a quick resolution of acute postoperative pain. On the day of surgery, these patients reported moderate pain intensity, which sharply decreased, and by the second postoperative day, their pain levels were notably reduced to no pain.

Slow Resolution Group:

Approximately 31.4% of the patients (N=128) demonstrated a steady decline in pain after surgery. They experienced moderate pain levels immediately post-surgery, and their pain level slightly increased the first day after surgery, but this pain consistently decreased with each subsequent day. By the fifth day after surgery, the pain level for these patients was zero.

Ongoing Pain Group:

About 20.6% of the patients (N=84) fell into the ongoing pain group. These patients began with moderate pain on the day of surgery. Their pain slightly increased the first and second day after surgery, and then gradually diminished. By the fifth postoperative day, patients in this category still had mild to moderate pain.

3.3.4.2 Association Between Trajectory Group Membership and Outcomes

The results showed significant differences in persistent pain experienced after hysterectomy surgery at both 2 weeks and 2 months post-surgery between different APSP trajectories ($p < 0.001$ at 2 weeks and $p = 0.026$ at 2 months). Additionally, the likelihood of 30-day readmission, prolonged opioid use at one week, 2 weeks and 2 months were significantly different among the three trajectories.

Table 3-6 Comparative Outcomes Across Three Pain Trajectories after Hysterectomy

Long term outcomes	Pain trajectories n (%)			
	Quick Resolution n=195	Slow Resolution n=128	Ongoing Pain n=84	p
Persistent post-hysterectomy pain at 2 weeks				
None	95(74.2)	136(69.7)	41(48.8)	
Mild (1-3)	24(18.8)	29(14.9)	22(26.2)	<0.001**
Moderate to severe (>=4)	9(7.0)	30(15.4)	21(25.0)	
Persistent post-hysterectomy pain at 2 month (+/- one week)				
None	102(79.9)	150(76.9)	54(64.3)	
Mild (1-3)	21(16.4)	25(12.8)	20(23.8)	0.026*
Moderate to severe (>=4)	5(3.9)	20(10.3)	10(11.9)	
30-day readmission				
Yes	11(8.6)	13(6.7)	14(16.7)	
No	117(91.4)	182(93.3)	70(83.3)	0.029*
Prolonged opioid use at 7 days after surgery				
Yes	1(0.8)	0(0)	16(19.0)	<0.001**
No	127(99.2)	195(100.0)	68(81.0)	
Prolonged opioid use at 2weeks after surgery				
Yes	7(5.5)	17(8.7)	13(9.1)	
No	121(94.5)	178(91.3)	71(90.9)	0.045*
Prolonged opioid use at 2 months after surgery				
Yes	5(3.9)	7(3.6)	9(10.7)	
No	123(96.1)	188(96.4)	75(89.3)	0.035*

*p<0.05

**p<0.01

After controlling for age, BMI, diagnosis, procedure, ASA class, anxiety diagnosis, neoadjuvant chemotherapy, preoperative opioid use and preoperative pelvic pain, the effect of different APSP trajectory membership is presented in **Table 3-7** based on generalized linear models. Results of full models including co-variates can be found in the **Appendix D** under

Supplementary Tables 2-7 the ongoing pain trajectory group(T3) was used as the referent group. Patients in the quick resolution trajectory (T1) had significantly lower persistent post-surgery pain at 2 weeks than T3(b =-0.99, p=0.02). At the two-month timepoint, the quick resolution (T1) and slow resolution (T2) groups had a reduced risk of persistent pain (b =-0.84, p=0.02 for T1; b =-1.36, p=0.01 for T2). Regarding 30-day readmissions, both patients in T1 and T2 were less likely to be readmitted than T3(b =-1.06, p=0.04 for T1; b =-1.97, p=0.01 for T2). There was no significant influence of trajectory group on prolonged opioid use at 2weeks or 2 months after surgery.

Table 3-7 Associations Between APSP Trajectories and Outcomes based on Generalized Linear Models

Long term outcomes Reference group: Trajectory 3 Ongoing Pain	Persistent post-hysterectomy pain at 2 weeks (Ordinal) b ± SE (p value)	Persistent post-hysterectomy pain at 2 months (Ordinal) b ± SE (p value）	30-day readmission Ref: No b ± SE (p value）	Prolonged opioid use at 7 days after surgery Ref: No b ± SE (p value）	Prolonged opioid use at 2 weeks after surgery Ref: No b ± SE (p value）	Prolonged opioid use at 2 months after surgery Ref: No b ± SE (p value）
Trajectory 1 Quick Resolution	**-0.99±0.32 (0.02)**	**-0.84 ±0.36 (0.02)**	**-1.06±0.50 (0.04)**	-17.93±5137 (0.997)	-0.86±0.53 (0.11)	-0.96±0.64 (0.13)
Trajectory 2 Slow Resolution	-0.52±0.49 (0.29)	**-1.36±0.52 (0.01)**	**-1.97±0.75 (0.01)**	-21.28±7602 (0.998)	-0.25±0.83 (0.77)	-0.99±1.05 (0.35)

3.3.5 Discussion

The primary aim of the study was to explore distinct acute post-operative pain trajectories over 5 days following a hysterectomy in patients with high-risk gynecological cancer and assess the associations between acute pain trajectories and 30-day readmission, persistent post-operative pain, and prolonged opioid use. While all trajectory groups reported moderate pain intensity immediately after hysterectomy (4-5 on a 0-10 scale), distinct trajectories of pain resolution emerged on post hysterectomy day 1. The study identified 3 distinct trajectories: the quick resolution group(T1), the slow resolution group(T2), and the ongoing pain group(T3). More than 50% of patients were in the slow resolution and ongoing pain groups. This is in contrast to our previous study about acute post-operative pain trajectories among all gynecological cancer patients where only 25% were in the slow resolution and ongoing pain group. In fact, 49.7 % of patients had no pain by post-operative day 1. These findings highlight the importance of sustained post-surgery pain management support in high-risk gynecologic cancer patients.

This study also reveals novel insights into the influence of distinct acute pain trajectories after hysterectomy on important post-discharge outcomes. Trajectory group membership was associated with persistent post-hysterectomy pain at both two weeks and two months post-surgery, 30-day readmission and prolonged opioid use at 1 week, 2 weeks, and 2 months after hysterectomy in bi-variate analyses. When controlling for variables such as age, BMI, diagnosis, and preoperative conditions, APSP trajectories still significantly predict persistent post-hysterectomy pain at 2 weeks and 2 months, and 30-day readmission. These results provide support for using APSP trajectories as an early indicator for poor outcomes that can help clinicians identify patients who need preventive interventions.

3.3.5.1 APSP trajectory and persistent pain after hysterectomy

Our study found strong relationships between being in the ongoing pain trajectory and the development of persistent post-surgical pain, even after controlling for perioperative factors. Many studies have suggested that APSP is closely related to persistent post-surgical pain. The intensity of APSP has been shown to be a major risk factor for CPSP in several studies (Nikolajsen & Minella, 2009; Theunissen et al., 2016). For example, VanDenKerkhof's cohort study found women with pain intensity >3/10 NRS at discharge had a higher risk of developing persistent pain after gynecological surgery. Instead of capturing APSP intensity at single time trajectory analyses capture information about both pain intensity and pain evolution over multiple post-operative days, which can help to predict persistent pain more precisely. A cohort study of patients with breast cancer seen in an emergency department found that patients with moderate to severe pain trajectories and those with severe-to-severe pain trajectory were more likely to develop chronic pain compared to patients in the low final pain trajectories (Okamoto et al., 2018). The study from Okamoto also demonstrated that there was higher precision in persistent pain prediction using acute pain trajectories compared to single time-point assessments. The strong association found between the ongoing pain trajectory and the presence of persistent pain adds weight to the hypothesis that there is a biological mechanism underlying the transition from acute to chronic post-operative pain. Ongoing or intense pain can lead to changes in both the peripheral and central nervous systems, which is known as pain sensitization and can cause the pain to become chronic(Chapman & Vierck, 2017).

3.3.5.2 APSP trajectory and 30-day readmission

Our study has uncovered a strong association between being in the ongoing acute pain trajectory and the likelihood of a patient being readmitted within 30 days, even after accounting for perioperative factors. This is particularly noteworthy in the context of gynecological oncology, where the rate of 30-day readmissions is approximately 11%(Wilbur et al., 2016). Among ovarian cancer patients, Henretta et al. (2011) documented that 10% were readmitted with pain as the primary indicator. The cost of these readmissions is a serious concern. On average, each readmission incurs a cost of $8059, and the average cost is $6199 for a pain indication readmission(Wilbur et al., 2016). Given the financial and clinical cost of readmissions within 30 days in gynecological oncology service, it is recognized as a critical measure of patient care quality and Medicare-based reimbursement. Therefore, understanding and addressing APSP trajectories, can have a dual advantage including improved patient outcomes and reduced unplanned readmissions in gynecologic oncology.

3.3.5.3 APSP trajectory and prolonged opioid use

Opioids are commonly used for alleviating postoperative pain following hysterectomy. However, prolonged opioid use has potential side effects like nausea, sedation, fatigue, and it might heighten the risk of addiction, bringing about both financial and social burden (Florence et al., 2016). A previous study revealed that over 6% of gynecological cancer patients continue to use opioids as long as six months after their hysterectomy (Swenson et al., 2018). Data suggests patients experiencing higher acute pain scores typically receive more extended and larger discharge opioid prescriptions, which may lead to prolonged opioid use. For example, Hsia et al. (2018) in their examination of 32,874 preoperative opioid users undergoing primary total knee

arthroplasty found that higher acute pain correlated with increased chronic significant opioid usage. A possible reason for this pattern may be related to prescribing practices. Surgeons typically prescribe opioid on the level of pain that patients report shortly after surgery. Nelson et al. (2019) implies that if a patient experiences high levels of pain in the immediate postoperative period, a surgeon may prescribe more opioids or extend the prescription duration to manage this pain. In our study, we found opioid use at 7 days, 2 weeks and 2 months are significantly different among the 3 distinct trajectory memberships, but when controlling for perioperative factors, the 3 trajectory memberships are no longer significant. This inconclusive result could likely be attributed to the limited sample size. Yet, to our understanding, these observations are among the first to pinpoint acute pain trajectories as potential risk factors for prolonged opioid usage. In conclusion, by sustained and personalized pain management, there might be a possibility to decrease long-term opioid consumption.

The present study had several limitations. First limitation is the scope of the study setting. As the research was conducted within a single university hospital, therefore, further validation in diverse settings and hospitals is crucial. Second, our data source primarily relied on retrospective information obtained from medical records and the Enhanced Recovery After Surgery (ERAS) dataset, which did not allow for a comprehensive assessment of pain. Additionally, frequent acute pain measurements were averaged into a single daily value in the ERAS dataset, potentially obscuring the nuances in pain experiences. Future research should aim to capture the dynamic nature of pain during the acute postoperative period more comprehensively, such as evaluating pain at various time intervals within a day. Moreover, distinguishing between different types of pain experiences, such as pain during movement versus pain at rest, average pain versus pain at worst could offer more profound insights into the patient's recovery journey and pain management

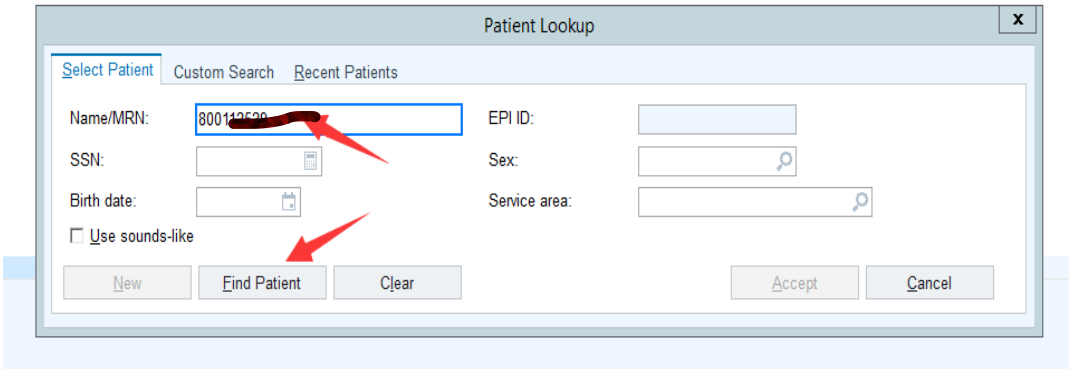
needs. Similarly, the assessment of persistent pain should be captured beyond medical records and assess the multifaced feature of persistent pain to better understand the transition from acute to chronic pain. This level of detail would greatly enrich our understanding of acute postoperative pain and inform better clinical practices moving forward.

In conclusion, the study underscores the significance of acute post-operative pain trajectories following hysterectomy in high-risk gynecological cancer patients. By identifying three distinct pain trajectories—quick resolution, slow resolution, and ongoing pain—the study highlighted the need for tailored post-operative pain management, especially in patients exhibiting ongoing pain patterns. These trajectories not only identified distinct patient recovery patterns but also serve as potential predictors for long-term outcomes such as persistent pain, 30-day readmissions, and prolonged opioid use. As healthcare stakeholders strive to deliver patient-centered care, recognizing these distinct trajectories can optimize recovery and minimize post-operative complications.

Appendix A Practice manual for data collection in medical records

Epicid

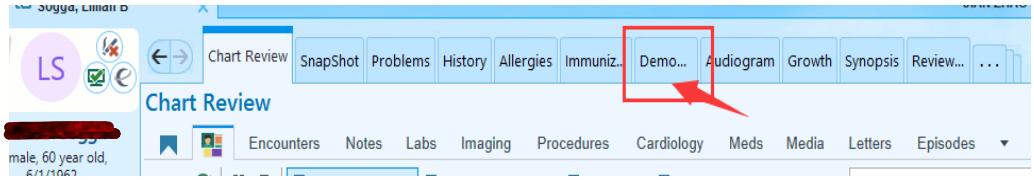
This variable is used to identify patients in Epic.

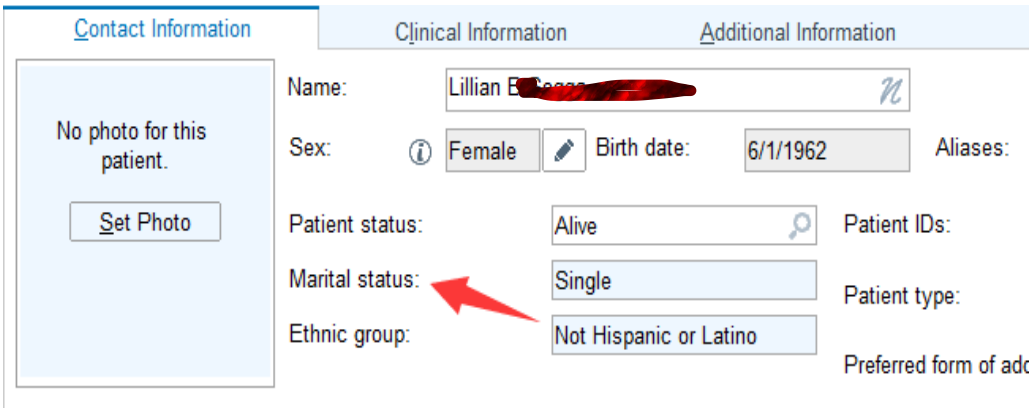


Marital_status

Step 1: Go to demographic tab

Step 2: 1-Single; 2-Married; 3-Widowed; 4-Divorced

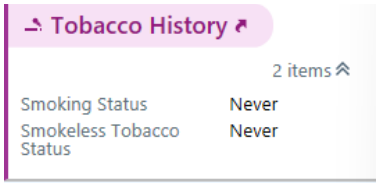




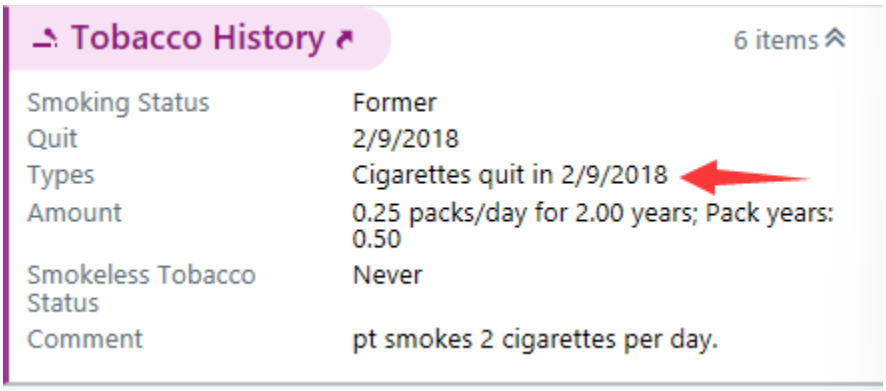
Smoking

On Chart Review page, tobacco history will show smoking status.

1-Never Smoker; 2-Former Smoker; 3-Current Smoker



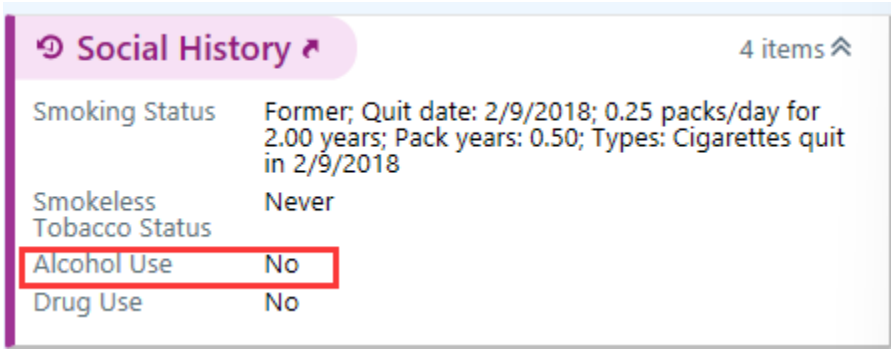
Notes: For former smokers, please check the date that patient quit smoking, if the date is after surgery date, we count the patient as current smoker.



Alcohol

On Chart Review page, social history will show alcohol use.

0-No; 1-Yes



Note: For a Not currently alcohol user, we count alcohol use as No.

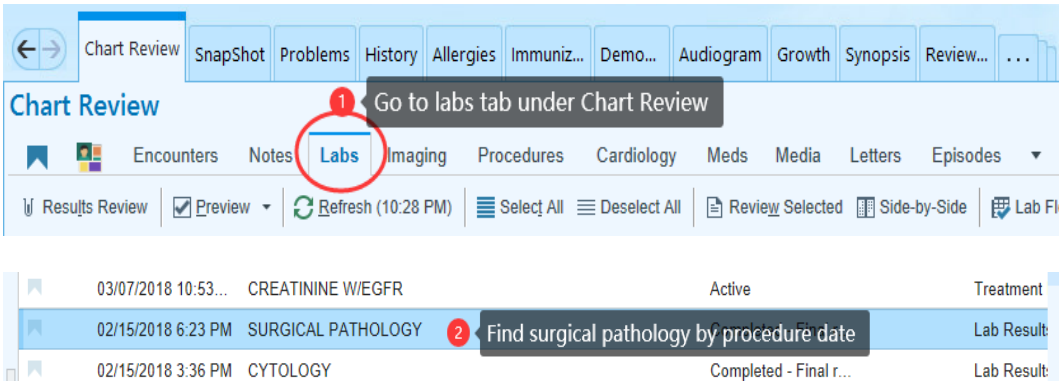
Diagnosis_code

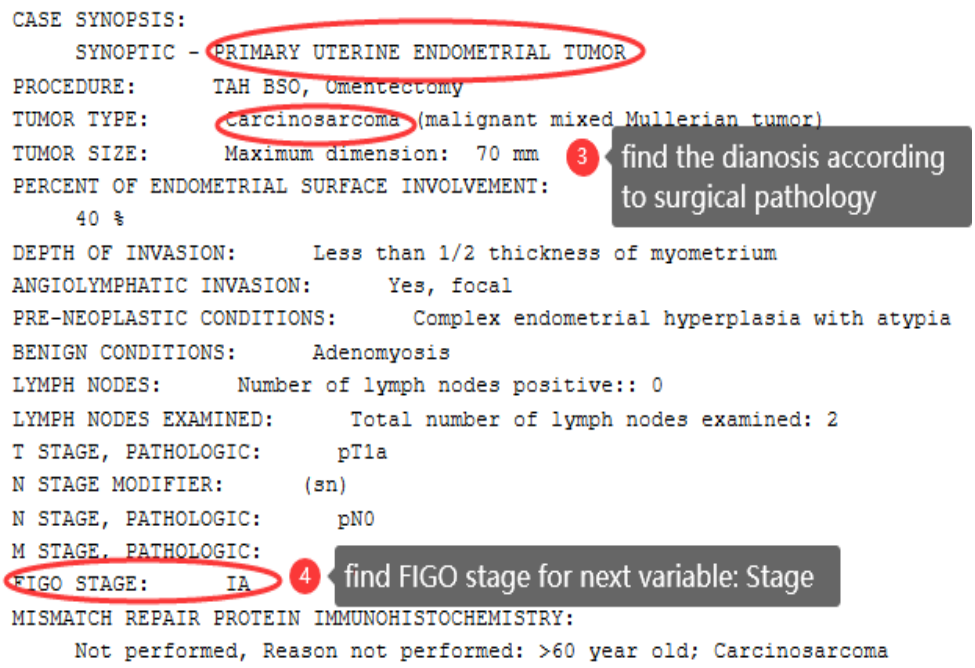
0-Endometrial cancer; 1-Ovarian Cancer; 2-Cervical Cancer; 3-Fallopian Tubal Cancer; 4-Peritoneal Cancer

The code of Diagnosis_code is based on the next variable Diagnosis.

Diagnosis

Find **surgical pathology** by surgery date:





Cancer_stage

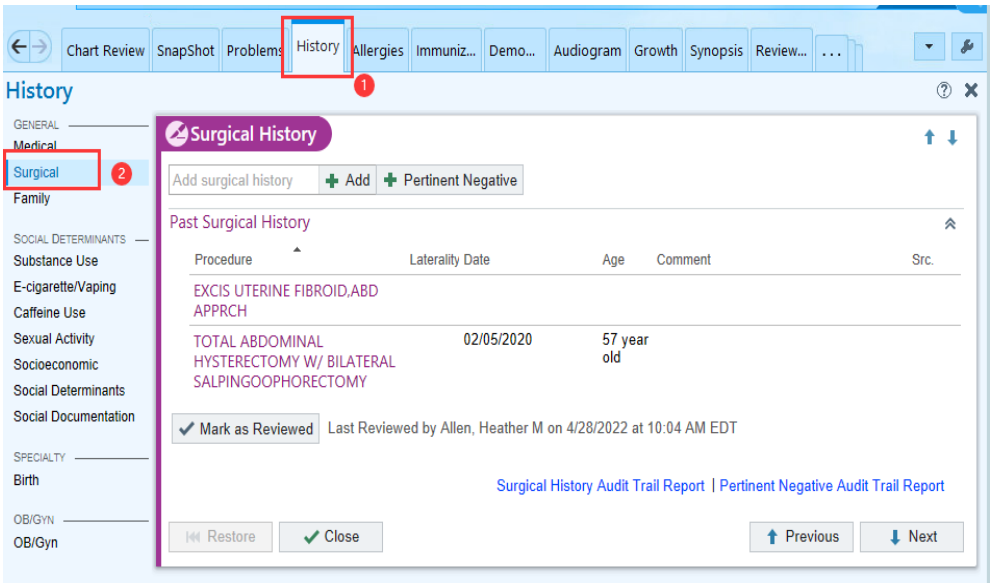
FIGO stage

See above about diagnosis

Cesarean_section_history

0-No; 1-Yes

Go to past surgical history and find out if there is Cesarean_section_history



Laparotomy_history

0-No; 1-Yes

See above about Cesarean_section_history

Laparoscopy_history

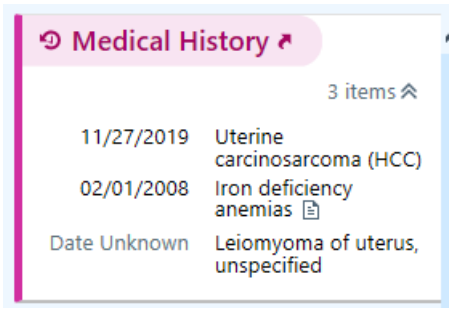
0-No; 1-Yes

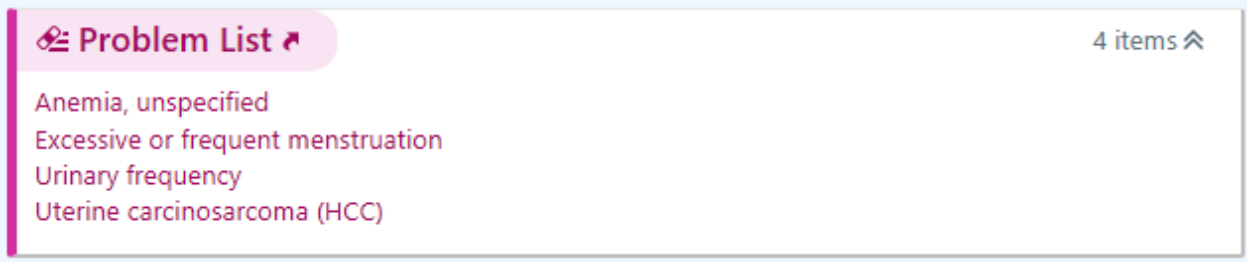
See above about Cesarean_section_history

anxiety_diagnosis

0-No; 1-Yes

Under SnapShot tab medical history and problem list, find diagnosis about anxiety





depression_diagnosis

0-No; 1-Yes

Under SnapShot tab medical history and problem list, find diagnosis about depression.

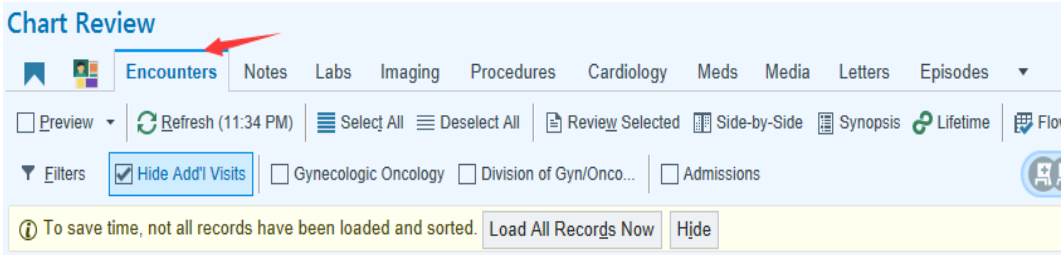
See above about anxiety_diagnosis

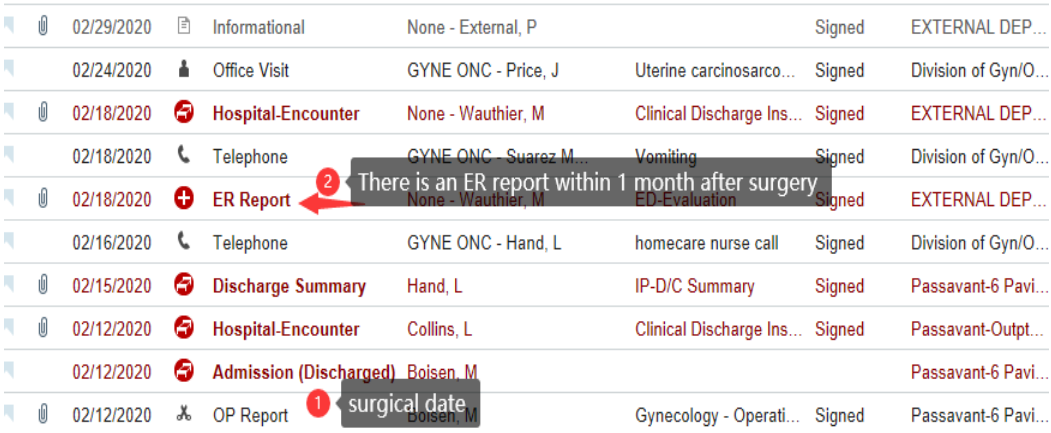
ERwithin1month

If patient has ER record within one month after the surgery

0-No; 1-Yes

In Chart Review-Encounters, find the surgical date and see if the following month (30 days) after surgery has any ER record





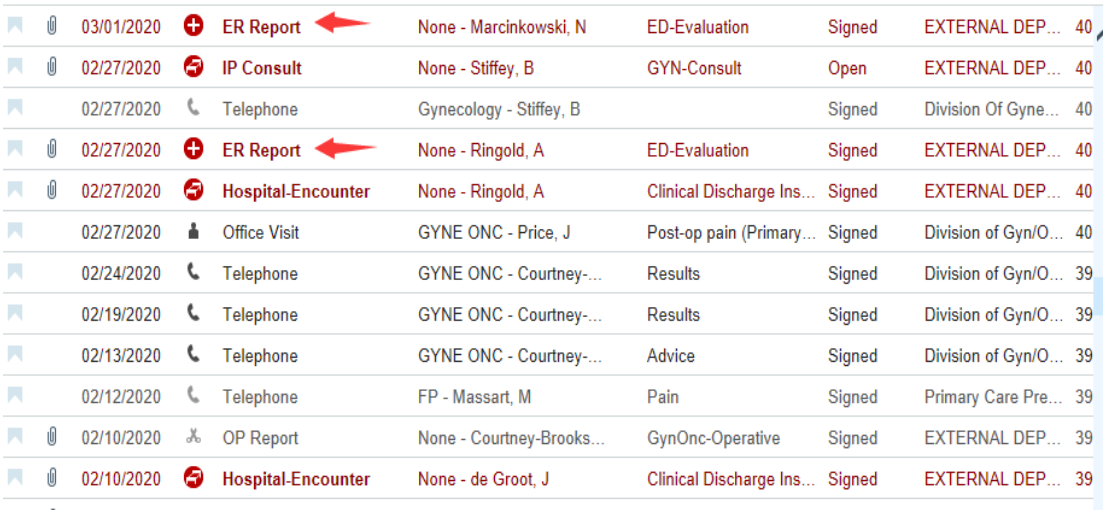
ERreason

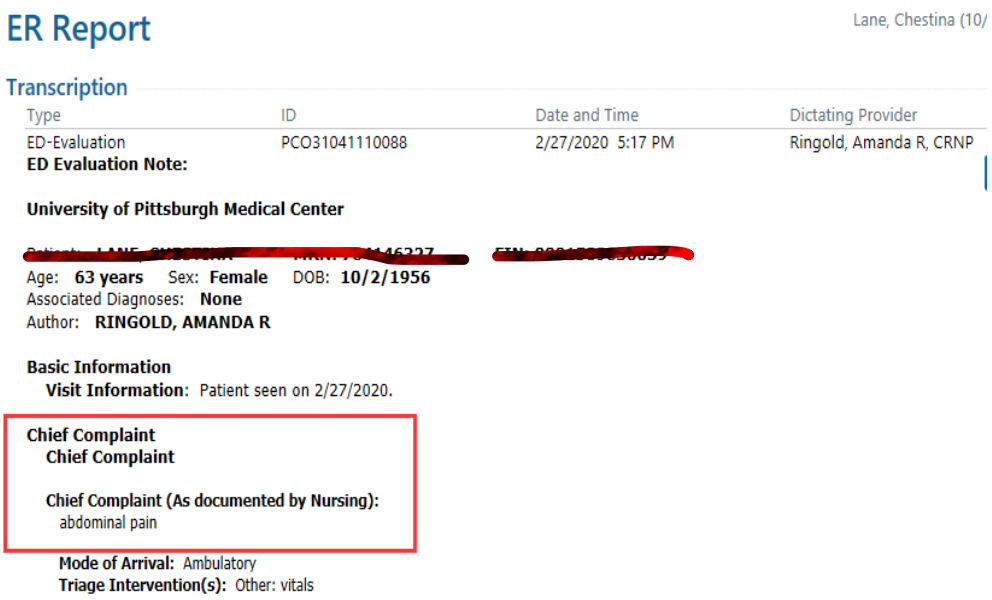
The reason for ER

-1: miss the reason for ER

-2: NOT applicable, patient does not have ER record within one month after surgery. When **ERwithin1month =0, ERreason=-2**

The information of ER reason could be gotten from ER report





ER Report

Lane, Chestina (10/

Transcription

Type	ID	Date and Time	Dictating Provider
ED-Evaluation	PCO31041110088	2/27/2020 5:17 PM	Ringold, Amanda R, CRNP

ED Evaluation Note:

University of Pittsburgh Medical Center

[redacted]

Age: **63 years** Sex: **Female** DOB: **10/2/1956**
Associated Diagnoses: **None**
Author: **RINGOLD, AMANDA R**

Basic Information
Visit Information: Patient seen on 2/27/2020.

Chief Complaint
Chief Complaint

Chief Complaint (As documented by Nursing):
abdominal pain

Mode of Arrival: Ambulatory
Triage Intervention(s): Other: vitals

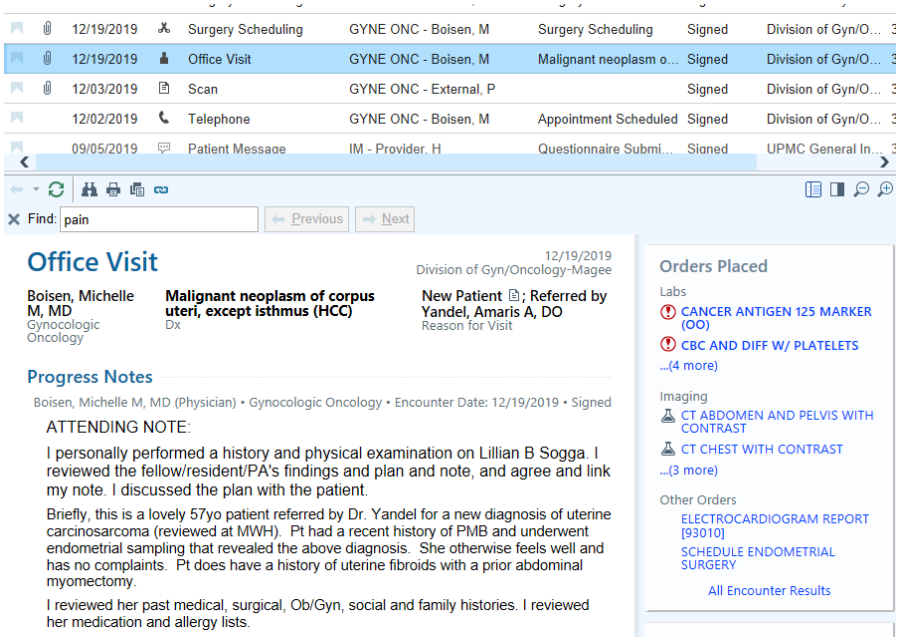
Preoppain

If patient has preoperative pelvic pain

0-No; 1-Yes

Go to patient's office visit before surgery and read patient's medical history

For example, after read through the office visit before surgery scheduling, patient did not mention any pelvic pain before surgery



Postop_visit1

The date of post visit near 2 weeks after surgery

Here we use Epicid 800112529 as an example, her surgery date is 02/12/2020

Postop_visit1 is the date near 2 weeks after 02/12/2020, and the office visit must be with **GYNE ONC**

Postoppain1

If patient has post-surgical pain (any mention about abdominal, pelvic or incisional pain)

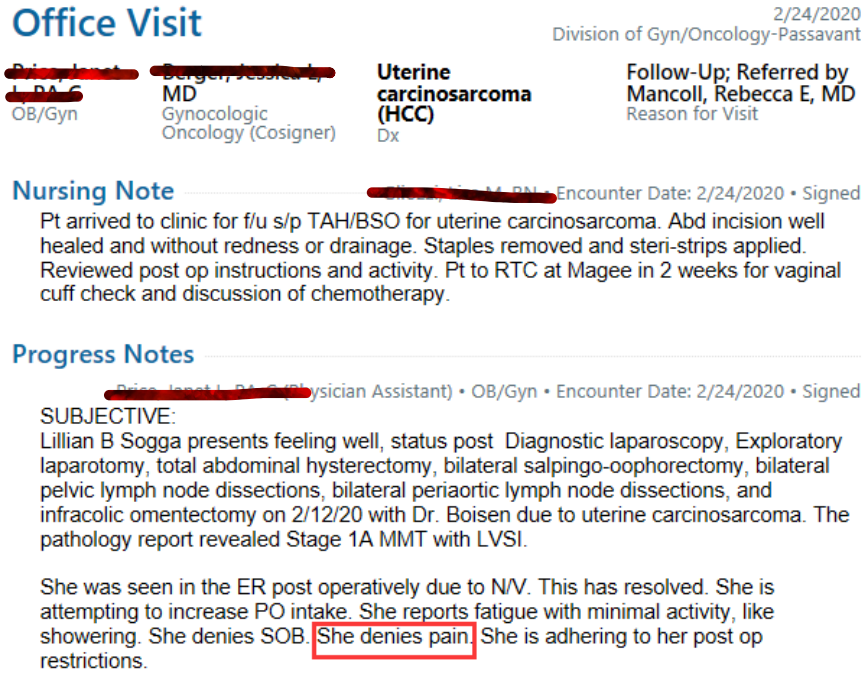
Read through the office visit on 02/24/2020 to see if there is any mention about abdominal, pelvic or incisional pain

0-No; 1-Yes

-1: Missing (have pain description but did not gave pain intensity in Epic)

-3: No office visit near 2 weeks after surgery

For Epicid 800112529, She denies pain.



Office Visit

2/24/2020
Division of Gyn/Oncology-Passavant

[redacted] MD
Gynecologic Oncology (Cosigner)

OB/Gyn

Uterine carcinosarcoma (HCC)
Dx

Follow-Up; Referred by Mancoll, Rebecca E, MD
Reason for Visit

Nursing Note [redacted] Encounter Date: 2/24/2020 • Signed

Pt arrived to clinic for f/u s/p TAH/BSO for uterine carcinosarcoma. Abd incision well healed and without redness or drainage. Staples removed and steri-strips applied. Reviewed post op instructions and activity. Pt to RTC at Magee in 2 weeks for vaginal cuff check and discussion of chemotherapy.

Progress Notes

[redacted] ysician Assistant) • OB/Gyn • Encounter Date: 2/24/2020 • Signed

SUBJECTIVE:
Lillian B Sogga presents feeling well, status post Diagnostic laparoscopy, Exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissections, bilateral periaortic lymph node dissections, and infracolic omentectomy on 2/12/20 with Dr. Boisen due to uterine carcinosarcoma. The pathology report revealed Stage 1A MMT with LVSI.

She was seen in the ER post operatively due to N/V. This has resolved. She is attempting to increase PO intake. She reports fatigue with minimal activity, like showering. She denies SOB. She denies pain. She is adhering to her post op restrictions.

Also, at the end of every visit, there is a pain assessment:

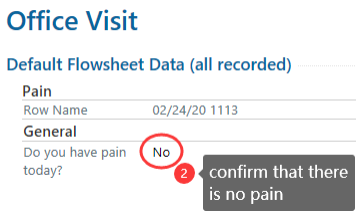
Additional Documentation

Vitals: BP 108/74 Pulse 98 Temp 98.1 °F (36.7 °C) (Oral) Resp 17
Wt 134 lb 6.4 oz (61 kg) BMI 24.19 kg/m² BSA 1.62 m²

Flowsheets: Vitals, Pain, Nutritional/FCN/Fall, Learning Needs and Cultural Concerns, *

Encounter Info: History, Allergies, Detailed Report, Billing Info, Patient Questionnaires, Flowsheets

1 click pain and see if there is any pain intensity



Office Visit

Default Flowsheet Data (all recorded)

Pain
Row Name 02/24/20 1113
General
Do you have pain today? No

2 confirm that there is no pain

Postop_Pain_location1

The location of pain

If **Postoppain1**=1(Yes), find the location of pain in office visit notes.

-1: Missing (patient has pain but did not have a record of pain location in Epic)

-2: Not applicable (patient did not have pain so not applicable for pain location). If **Postoppain1**=0(No), **Postop_Pain_location1 =-2**

-3: No office visit near 2 weeks after surgery

Postop_Pain_intensity1

Postop pain intensity at post visit near 2 weeks after surgery

Usually Additional document-Pain would show pain intensity range from 0-10

-1: Missing (have pain description but did not gave pain intensity in Epic)

-3: No office visit near 2 weeks after surgery

Postop_Pain_description1

Any description about post op pain at office visit near 2 weeks after surgery

Read through office visit, record any description about post-surgical pain (any description about abdominal, pelvic or incisional pain).

-1: Missing (patient has pain but did not have pain description in Epic, only gave pain intensity)

-2: Not applicable (patient did not have pain so not applicable for pain description). If **Postoppain1**=0(No), **Postop_Pain_description1=-2**

-3: No office visit near 2 weeks after surgery

Other_pain1:

If patients have other source of pain at 2 weeks

Read through the office visit and see if the patient has other source of pain.

0-No; 1-Yes

-3: No office visit near 2 weeks after surgery

Other_pain_description1

description of other source of pain at 2 weeks

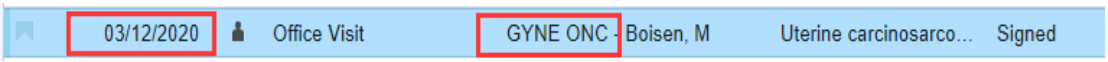
-2: Not applicable (patient did not have other source of pain so not applicable for **Other_pain_description1**). If **Other_pain1=0(No), Other_pain_description1=-2**

-3: No office visit near 2 weeks after surgery

Postop_visit2

The date of post visit near 1 month after surgery

Postop_visit2 is the date near 4 weeks (1 month) after 02/12/2020, and the office visit must be with **GYNE ONC**



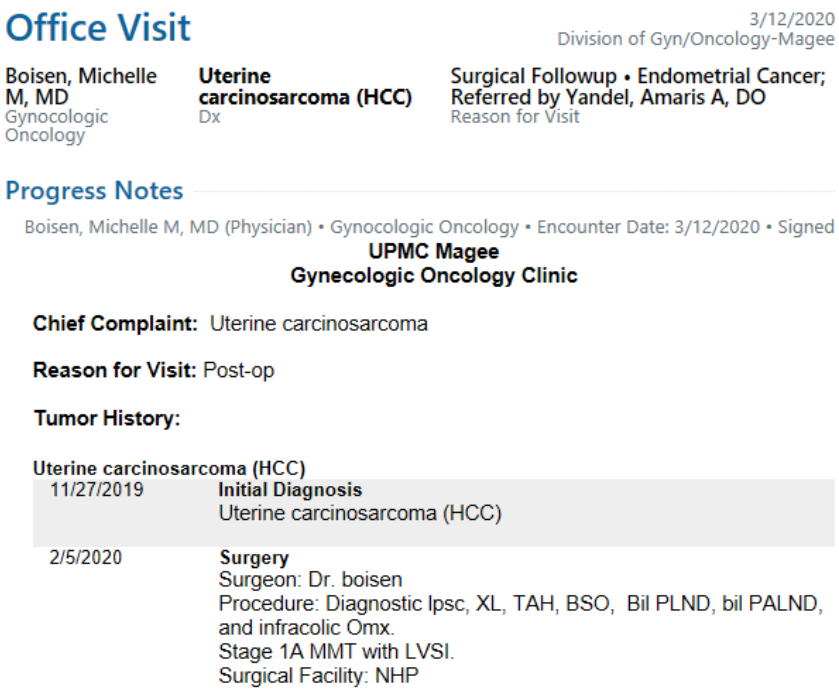
If patient has post-surgical pain (any mention about abdominal, pelvic or incisional pain)

Read through the office visit on 03/12/2020 to see if there is any mention about abdominal, pelvic or incisional pain

0-No; 1-Yes

-1: Missing (have pain description but did not gave pain intensity in Epic)

-3: No office visit near 4 weeks after surgery



Office Visit

3/12/2020
Division of Gyn/Oncology-Magee

Boisen, Michelle M, MD	**Uterine carcinosarcoma (HCC)**	Surgical Followup • Endometrial Cancer; Referred by Yandel, Amaris A, DO
Gynocologic Oncology	Dx	Reason for Visit

Progress Notes

Boisen, Michelle M, MD (Physician) • Gynocologic Oncology • Encounter Date: 3/12/2020 • Signed

UPMC Magee
Gynecologic Oncology Clinic

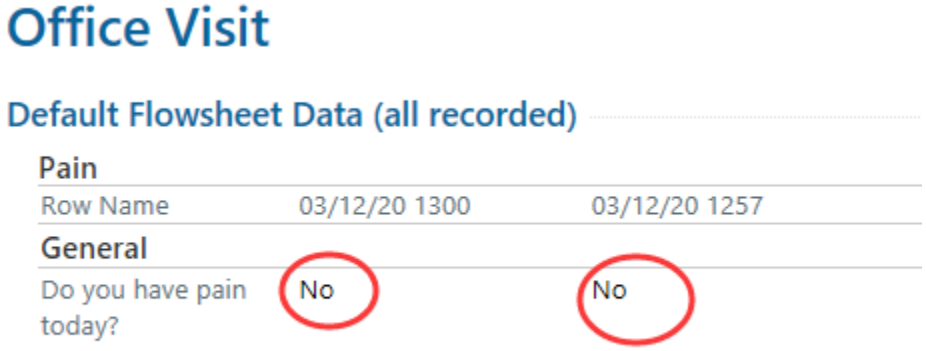
Chief Complaint: Uterine carcinosarcoma

Reason for Visit: Post-op

Tumor History:

Uterine carcinosarcoma (HCC)

11/27/2019	**Initial Diagnosis** Uterine carcinosarcoma (HCC)
2/5/2020	**Surgery** Surgeon: Dr. boisen Procedure: Diagnostic lpsc, XL, TAH, BSO, Bil PLND, bil PALND, and infracolic Omx. Stage 1A MMT with LVSI. Surgical Facility: NHP



Office Visit

Default Flowsheet Data (all recorded)

Pain

Row Name	03/12/20 1300	03/12/20 1257
General		
Do you have pain today?	No	No

Postop_Pain_location2, Postop_Pain_intensity2, Postop_Pain_description2, Other_pain2, Other_pain_description2

Read through the office visit on 3/12/2020

See above from Postop_Pain_location1 to Other_pain_description1

Postop_visit3

The date of post visit near 2 months after surgery

Postop_visit3 is the date near 2 months after 02/12/2020, and the office visit must be with **GYNE ONC**

05/19/2020	Treatment Protocol	GYNE ONC - Boisen, M		Open	Division of Gyn/O...
04/30/2020	Infusion	INFUSION CEN - AREA...	Treatment	Signed	Magee Womens...
04/30/2020	Unknown	BOISEN, MICHELLE M			
04/28/2020	Treatment Protocol	GYNE ONC - Boisen, M		Open	Division of Gyn/O...
04/27/2020	Telephone	GYNE ONC - Boisen, M		Signed	Division of Gyn/O...
04/24/2020	Telephone	GYNE ONC - Boisen, M		Signed	Division of Gyn/O...
04/23/2020	Telephone	GYNE ONC - Boisen, M		Signed	Division of Gyn/O...
04/23/2020	Telephone	GYNE ONC - Boisen, M	Oncology Navigation...	Signed	Division of Gyn/O...
04/20/2020	Telephone	GYNE ONC - Boisen, M		Signed	Division of Gyn/O...
04/14/2020	Telephone	GYNE ONC - Boisen, M		Signed	Division of Gyn/O...
04/09/2020	Telephone	GYNE ONC - Boisen, M		Signed	Division of Gyn/O...
04/02/2020	Telephone	GYNE ONC - Boisen, M		Signed	Division of Gyn/O...

There is no office visit near 2 months after the surgery date 02/12/2020

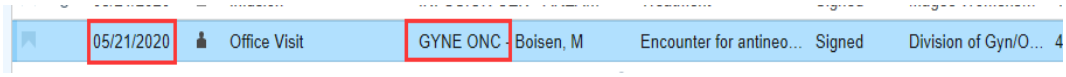
Postoppain3, Postop_Pain_location3, Postop_Pain_intensity3, Postop_Pain_description3, Other_pain3, Other_pain_description3

See above from Postoppain1 to Other_pain_description1

Postop_visit4

The date of post visit near 3 months after surgery

Postop_visit4 is the date near 3 months after 02/12/2020, and the office visit must be with **GYNE ONC**



05/21/2020	Office Visit	GYNE ONC - Boisen, M	Encounter for antineo...	Signed	Division of Gyn/O...	4

Postoppain4

If patient has post-surgical pain (any mention about abdominal, pelvic or incisional pain)

Read through the office visit on 05/21/2020 to see if there is any mention about abdominal, pelvic or incisional pain

0-No; 1-Yes

-1: Missing (have pain description but did not gave pain intensity in Epic)

-3: No office visit near 4 weeks after surgery

In our example, the patient did not have any pain about abdominal, pelvic or incisional pain, but she had leg pain which might associated with chemotherapy.

No change in past medical, family or social history.

Interval History
Tolerated cycle 1 well. Had a few days of fatigue and leg pain - thought it might be r/t drinking a lot of coffee. Also has hair loss and some mild constipation. No other side effects
No neuropathy. Denies CP/SOB, vaginal bleeding.
Complaint with premed

Postop_Pain_location4, Postop_Pain_intensity4, Postop_Pain_description4, Other_pain4, Other_pain_description4

Read through the office visit on 5/21/2020

See above from Postop_Pain_location1 to Other_pain_description1

Note: if the patient has post-op pain at 3 months (**Postoppain4=1**), read the following office visits at 4 months, 5 months and 6 months to see if patient still mentioned about post-op abdominal pain.

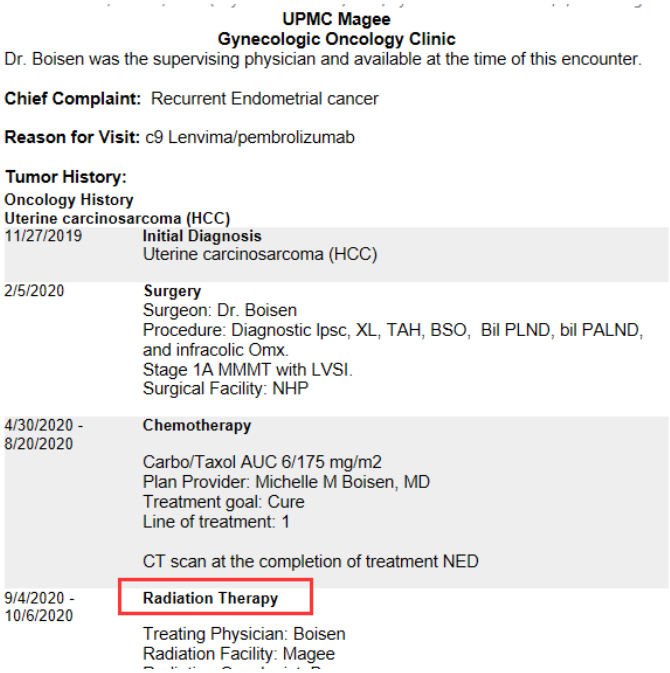
If patients do not have office visit at 3 months, find the nearest visit after 3 month and see if patient have post-op chronic pain. For example, for 784146327 (C.L.), we used a 4-month office visit on 6/16/2020 that documented no post-op pain.

Radiotherapy

0-No; 1-Yes

If patient has radio therapy or not

Read the nearest office visit and see if patients have radiation therapy in progress notes



UPMC Magee
Gynecologic Oncology Clinic

Dr. Boisen was the supervising physician and available at the time of this encounter.

Chief Complaint: Recurrent Endometrial cancer

Reason for Visit: c9 Lenvima/pembrolizumab

Tumor History:

Oncology History
Uterine carcinosarcoma (HCC)

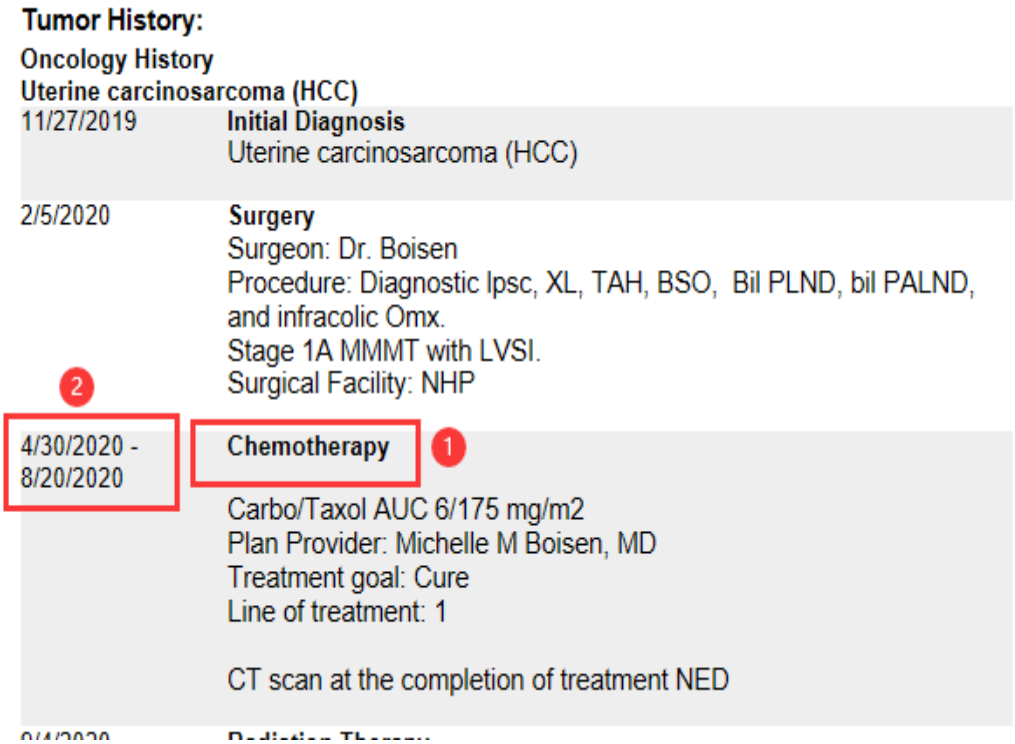
11/27/2019	**Initial Diagnosis** Uterine carcinosarcoma (HCC)
2/5/2020	**Surgery** Surgeon: Dr. Boisen Procedure: Diagnostic lpsc, XL, TAH, BSO, Bil PLND, bil PALND, and infracolic Omx. Stage 1A MMMT with LVSI. Surgical Facility: NHP
4/30/2020 - 8/20/2020	**Chemotherapy** Carbo/Taxol AUC 6/175 mg/m2 Plan Provider: Michelle M Boisen, MD Treatment goal: Cure Line of treatment: 1 CT scan at the completion of treatment NED
9/4/2020 - 10/6/2020	**Radiation Therapy** Treating Physician: Boisen Radiation Facility: Magee

Chemotherapy

0-No; 1-Yes

If patient has chemotherapy or not

Read the nearest office visit and see if patients have chemotherapy in progress notes



First_chemo_date

If the patient has chemotherapy, record the first date of chemotherapy. In our example, it is 4/30/2020.

See chemotherapy variable above

anxiety_visit1

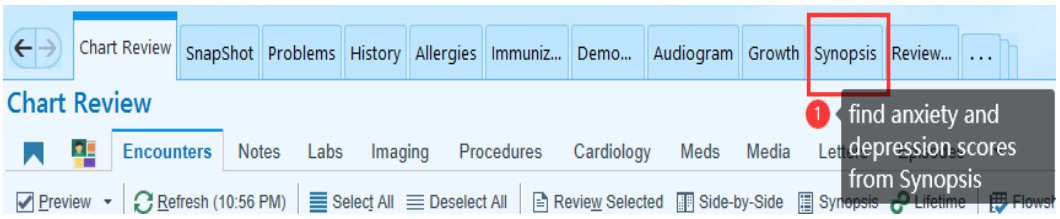
anxiety level (from 0-10) near the date of "Postop_visit1"(2 weeks after surgery) from Synopsis tab PRICIS questionnaires

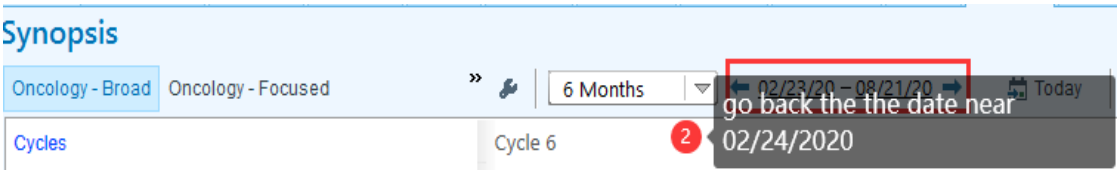
In our example, we will find anxiety score near 02/24/2020

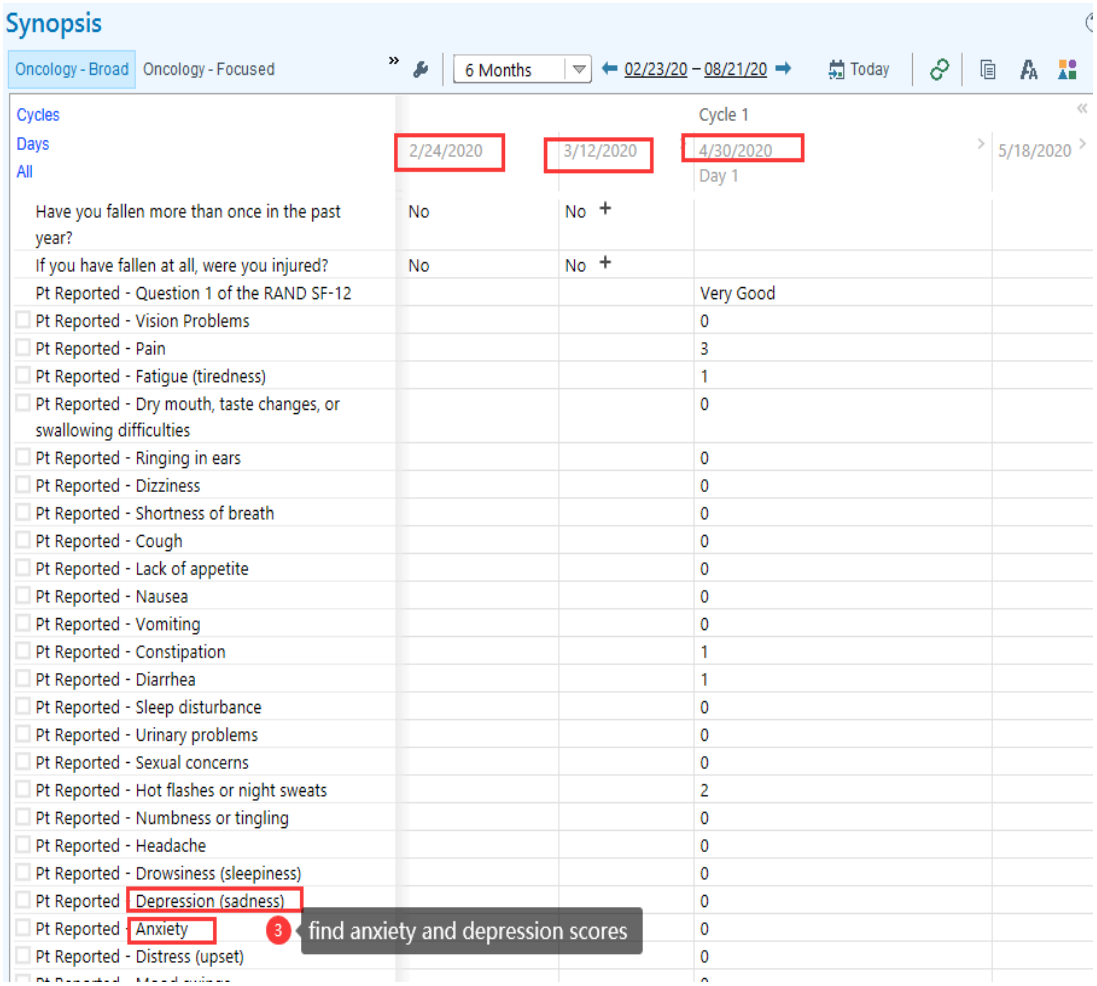
-1 Missing (already started chemo but did not have anxiety assessment near 1 month after surgery)

-2 Not applicable (Did not have chemo at this visit so do not have anxiety assessment)

-3 do not have office visit at the corresponding office visit







anxiety_visit2

anxiety level (from 0-10) near the date of "Postop_visit2"(1 month after surgery) from Synopsis tab PRICIS questionnaires

In our example, we will find anxiety score near 03/12/2020

See anxiety visit 1 above.

anxiety_visit3

Anxiety level (from 0-10) near the date of "Postop_visit3"(2 months after surgery) from Synopsis tab PRICIS questionnaires

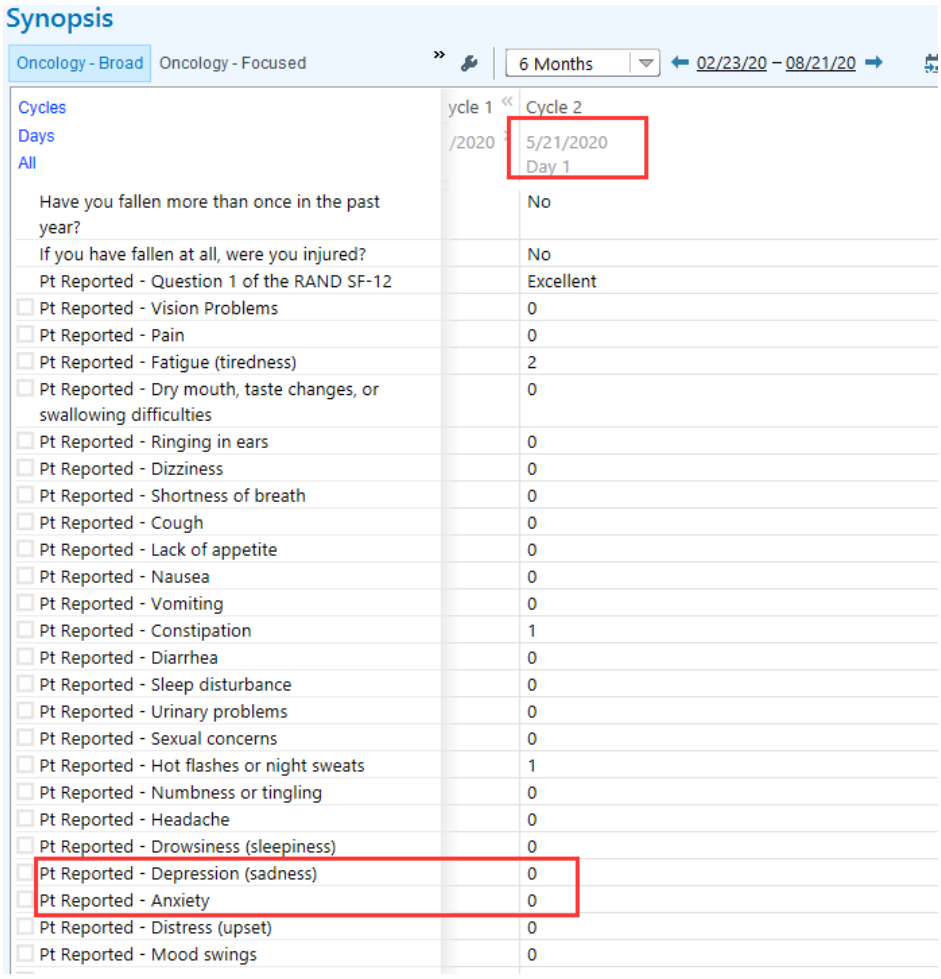
In our example, we need to find anxiety score near office visit 3, but we do not have office visit at 2 months after surgery. -3 for do not have office visit at the corresponding office visit

See anxiety_visit 1 above

anxiety_visit4

Anxiety level (from 0-10) near the date of "Postop_visit4"(3 months after surgery) from Synopsis tab PRICIS questionnaires

See anxiety_visit 1 above



depression_visit1, depression_visit2, depression_visit3, depression_visit4

see anxiety_visit1 to anxiety_visit4 above.

deceased

0- No; 1-Yes

Appendix B Supplementary table for Manuscript #1

Authors and years	Demographic	Psychological factors	Surgical related	Pain related	Others
Benign condition					
(Brandsborg et al., 2007)			Significant: previous cesarean delivery, type of anesthesia (spinal anesthesia), Hysterotomy indication-pain Non-significant: type of hysterotomy, epidural during surgery, post operative analgesic	Significant: preoperative pelvic pain, pain problems elsewhere	
(Pinto et al., 2012)	Significant: age	Significant: presurgical anxiety, postsurgical anxiety, emotional illness representation, and pain catastrophizing Non-significant: Presurgical fear	Significant: type of hysterectomy (open abdominal hysterectomies)	Significant: Acute postsurgical pain frequency, pain problems elsewhere Non-significant: Previous presurgical pain, Acute postsurgical pain intensity	

(Pinto, McIntyre, Araújo-Soares, et al., 2018)	Significant: Disease onset (months) Non-significant: BMI	Significant: presurgical anxiety, postsurgical anxiety, long term consequences of surgical fear, emotional illness representation , pain catastrophizing Non-significant: presurgical depression, immediate consequences of surgical fear, life orientation-optimism, illness perception, coping strategies	Significant: type of hysterectomy (open abdominal hysterectomies), type of incision-Pfannenstiel incision Non-significant: previous abdominal surgery, uterus weight, uterus height	Significant: preoperative pelvic pain, Acute postsurgical pain intensity, Acute postsurgical pain frequency Non-significant: Pain problems elsewhere	Significant: Non-significant: psychotropic use, length of stay
(Montes et al., 2015)	The risk factor is not specific for hysterectomy but also include hernia repair and thoracotomy				
(Pokkinen et al., 2015)	Significant: Smoking Non-significant: age		Significant: type of hysterectomy(laparoscopic) Non-significant: surgical related infection, type of anesthesia	Significant: Acute postsurgical pain intensity	Non-significant: Remifentanil consumption

(Theunissen et al., 2016)	Significant: Non-significant: hospitals, age, number of close friends/relatives,	Significant: surgery-related worries Non-significant: expectations about hysterectomy (relief/neutral/loss), general psychological robustness,	Significant: surgery-related infection[¥] Non-significant: type of anesthesia, type of incision, ASA classification, having undergone prolapse surgery	Significant: preoperative pelvic pain, Acute postsurgical pain intensity Non-significant: pain problems elsewhere, expected Acute postsurgical pain,	Significant: Non-significant: gravidity
(Beyaz, Özocak, et al., 2016)	Significant: Non-significant:	Significant: Non-significant:	Significant: Non-significant: Hysterotomy indication, previous abdominal surgery, previous cesarean delivery, type of incision, incision length	Significant: Non-significant:	Significant: Sensorial alterations as hypoesthesia and hyperesthesia around abdominal scar Non-significant:
(Han et al., 2017)	Significant: Non-significant: Age, education, employment, BMI, Smoking, Alcohol	Significant: presurgical anxiety, presurgical depression Non-significant:	Significant: Non-significant: ASA classification, Hysterotomy indication, hypertension, diabetes, coronary heart disease, previous cesarean delivery, previous abdominal surgery, type of incision, type of anesthesia,	Significant: preoperative pain, Acute postsurgical pain intensity at movement Non-significant: Acute postsurgical pain intensity at rest	Significant: Sexual satisfaction Non-significant: Preoperative analgesic, post operative analgesic

			blood infusion, blood loss, length of surgery		
(Sng et al., 2018c)	Significant: Non-significant:	Significant: Pain catastrophizing, presurgical trait anxiety Non-significant: presurgical state anxiety	Significant: intraoperative morphine consumption Non-significant: Intraoperative fentanyl	Significant: preoperative pelvic pain, preoperative pain during sexual intercourse Acute postsurgical pain intensity at rest, Acute postsurgical pain during coughing and itching Non-significant:	Significant: mechanical temporal summation score Non-significant:
(Jin et al., 2020)			Non-significant: type of hysterectomy		
(As-Sanie et al., 2019)	Significant: Non-significant: Age, race,	Significant: Non-significant: presurgical depression, presurgical anxiety	Significant: Non-significant: type of hysterectomy , pelvic adhesions, uterine weight, adenomyosis on histopathology	Significant: preoperative centralized pain scores Non-significant: average pain severity during menses, average overall pelvic pain, pain duration before surgery	Significant: endometriosis, uterine fibroids Non-significant:
(Hoofwijk et al., 2019)	Significant: Employment	Significant: Non-significant:	Significant: Non-significant:	Significant: preoperative hysterectomy-related pain, neuropathic pain at post-operative day 4	Significant: self-reported infection at first 3 months, rs4818(COMT gene)

	Non-significant: age	Surgical-related worries		Non-significant: Pain problems elsewhere	Non-significant: gravidity
(Tan et al., 2020)-4 months after surgery	Significant: Non-significant: Age, BMI, race, education,	Significant: Pain catastrophizing, PCS-rumination score, PCS-helpless score total SATI socres, trait anxiety Non-significant: state anxiety, PCS-magnification score	Significant: Previous surgery at abdominal or pelvic region Non-significant: type of hysterectomy	Significant: Non-significant: Presence of preoperative pain in lower abdomen, Presence of pain during sexual intercourse	Significant: mechanical temporal summation magnitude, Presence of evoked MTS Non-significant:
(Tan et al., 2020)-6 months after surgery	Significant: Non-significant: Age, BMI, race, education,	Significant: Pain catastrophizing, PCS-rumination score, PCS-helpless score Non-significant: state anxiety, total SATI scores, trait anxiety	Significant: Non-significant: Previous surgery at abdominal or pelvic region, type of hysterectomy	Significant: Non-significant: Presence of preoperative pain in lower abdomen, Presence of pain during sexual intercourse	Significant: mechanical temporal summation score Non-significant: Presence of evoked MTS
Grundström et al., 2022)	Significant: age, smoking, employed	Significant: Non-significant:	Significant: Hysterectomy indication-bleeding disorder, type of surgery(abdominal), type of anesthesia,	Significant: Non-significant:	Significant: Bleeding complications within 8 weeks after discharge, Infection complications within

	Non-significant: BMI		Non-significant: ASA class, hysterectomy type (total vs subtotal), Bilateral oophorectomy,		8 weeks after discharge, Micturition complications within 8 weeks after discharge, Endometriosis Non-significant: parity, Complications during hospital stay.
Cancer					
(Sørensen et al., 2015)	Significant: Non-significant: age	Significant: Non-significant:	Significant: lower blood loss, operation time Non-significant: surgery type,	Significant: preoperative operative pain, acute postoperative pain intensity Non-significant: preoperative pain elsewhere	Significant: Non-significant:
(Lunde et al., 2019)	Significant: BMI	Significant:	Significant:	Significant: preoperative heat pain hyperalgesia, preoperative pelvic pain, acute postoperative pain intensity	Significant:
(Saxena et al., 2016)	Significant: Non-significant:	Significant: Non-significant:	Significant: Non-significant:	Significant: Non-significant:	Significant: Up-regulation in the mRNA expression of signal transduction genes

Appendix C Supplementary materials for Manuscript #2

Tables 1 and Table 2 show the process for selection of different trajectory shapes (e.g., linear, quadratic, cubic). By comparing different trajectory shapes based on their BIC values, we chose three specific shapes with the smallest BICs. Then the study further assessed the AvePP value of the three specific shapes and ultimately the trajectory shape labeled as (1 2 2 2) was chosen. Mean fit estimates for the selected model of 4 trajectory groups were excellent: 0.89 for no pain group, 0.95 for rapid resolution group, 0.98 for slow resolution group and 0.97 for ongoing pain group.

Supplementary Table 1. BICs for different trajectory shapes

Number of groups	Trajectory shapes *	BIC(N=1323)
2	3 3	-7992.08
2	2 2	-7988.85
2	1 2	-8066.37
2	1 3	-8069.96
3	3 3 3	-7963.13
3	2 2 2	-7956.26
3	1 2 2	-7950.48
3	0 2 2	-7956.69
3	0 1 2	-7876.21
3	0 1 1	-8029.67
4	2 2 2 2	-7650.21
4	**1 2 2 2**	**-7646.62**
4	0 2 2 2	-7652.59
4	0 1 2 2	-7675.53

*For trajectory shapes, 0-intercept, 1-Linear, 2- Quadratic, 3- Cubic

Supplementary Table 2. AvePP values for the 3 shapes with similar BICs

	Group1	Group2	Group3	Group4	BIC(N=1323)
2 2 2 2	0.88	0.95	0.98	0.96	-7650.21
1 2 2 2	**0.89**	**0.95**	**0.98**	**0.97**	**-7646.62**
0 2 2 2	0.91	0.95	0.98	0.96	-7652.59

BIC=−2×log-likelihood+ (the number of parameters) ×log (sample size). BIC (n=407) represents as sample size-adjusted BIC.

Supplementary Table 3 Variance Inflation Factor (VIF) Among Baseline Factors

Baseline Factors	VIF
BMI	1.15
CCI Scores	1.10
Surgery procedure time (in minutes)	1.30
Diagnosis- (reference: endometrial cancer)	
Ovarian/ Fallopian tubal/Peritoneal cancer	1.89
Cervical cancer	1.04
Smoking- (reference: Never smoker)	
Former Smoker	1.05
Current Smoker	1.06
Cancer stage- (reference: I)	
II	1.07
III	1.07
IV	1.09
Laparotomy history-Yes (vs no)	1.06
Laparoscopy history- Yes (vs no)	1.05
Anxiety diagnosis- Yes (vs no)	1.18
Preoperative pelvic pain- Yes (vs no)	1.12
Preoperative opioid use- Yes (vs no)	1.25
Surgery Procedure- (reference: minimal invasive hysterectomy)	
Total abdominal hysterectomy	2.00
ASA class- >=3(vs <=2)	1.13

Appendix D Supplementary materials for Manuscript #3

Supplementary table1- BICs for the selection of best trajectory model

Number of groups	Trajectory shapes *	BIC(N=407)
2	3 3	3401.97
2	2 2	3397.20
2	1 2	3462.65
3	3 3 3	3249.14
3	2 2 2	3243.74
3	1 2 2	3391.30
3	0 2 2	3404.30
3	0 1 2	3356.11
3	0 1 1	3353.13
4	2 2 2 2	3323.49
4	1 2 2 2	3446.27
4	0 2 2 2	3443.25
4	0 1 2 2	3467.97

BIC=−2×log-likelihood+ (the number of parameters) ×log (sample size). BIC (n=407) represents as sample size-adjusted BIC.

Supplementary table2-GLM for Persistent post-hysterectomy pain at 2 weeks

	B	95% Wald Confidence Interval	p
Age	-0.023	[-0.043, -0.003]	0.027*
BMI	-0.004	[-0.022, 0.014]	0.649
Diagnosis (Ref: Ovarian/ Fallopian tubal/Peritoneal cancer)			
Endometrial cancer	-0.384	[-0.938, 0.170]	0.175
Procedure (Ref: Total abdominal hysterectomy)			
Minimally invasive surgery	0.165	[-0.693,1.024]	0.706
ASA class (Ref: ASA>=3)			
ASA<=2	-0.041	[-0.511,0.430]	0.865
Anxiety diagnosis (Ref: Yes)			
No	-0.424	[-0.917,0.068]	0.091
Neoadjuvant chemotherapy (Ref: Yes)			
No	0.824	[0.013,1.635]	0.046*
Preoperative opioid use (Ref: Yes)			
No	-0.154	[-0.639,0.331]	0.534
Preoperative pelvic pain (Ref: Yes)			
No	-0.331	[-0.809,0.146]	0.174
Trajectory group (Ref: Ongoing pain)			
Rapid Resolution	-0.991	[-1.622, -0.375]	0.020*
Slow Resolution	-0.522	[-1.479, 0.435]	0.285

Likelihood Ratio Chi-Square for the overall model is 31.716 with $p<0.001$.

Supplementary table3-GLM for Persistent post-hysterectomy pain at 2 months

	B	95% Wald Confidence Interval	p
Age	-0.017	[-0.038, 0.005]	0.129
BMI	0.001	[-0.012, 0.013]	0.906
Diagnosis (Ref: Ovarian/ Fallopian tubal/Peritoneal cancer)			
Endometrial cancer	0.596	[-0.037, 1.230]	0.065
Procedure (Ref: Total abdominal hysterectomy)			
Minimally invasive surgery	0.785	[-0.128,1.643]	0.094
ASA class (Ref: ASA>=3)			
ASA<=2	-0.214	[-0.739,0.312]	0.426
Anxiety diagnosis (Ref: Yes)			
No	-0.040	[-0.588,0.508]	0.886
Neoadjuvant chemotherapy (Ref: Yes)			
No	0.082	[-0.800,0.963]	0.856
Preoperative opioid use (Ref: Yes)			
No	0.055	[-0.494,0.605]	0.844
Preoperative pelvic pain (Ref: Yes)			
No	-0.376	[-0.909,0.157]	0.166
Trajectory group (Ref: Ongoing pain)			
Rapid Resolution	-0.841	[-1.548, -0.133]	0.020*
Slow Resolution	-1.358	[-2.388, -0.328]	0.010*

Likelihood Ratio Chi-Square for the overall model is 18.556 with p=0.070.

Supplementary table4-GLM for 30-day readmission (Ref: No)

	B	95% Wald Confidence Interval	p
Age	-0.001	[-0.034, 0.032]	0.953
BMI	0.006	[-0.007, 0.020]	0.357
Diagnosis (Ref: Ovarian/ Fallopian tubal/Peritoneal cancer)			
Endometrial cancer	0.796	[-0.118, 1.709]	0.088
Procedure (Ref: Total abdominal hysterectomy)			
Minimally invasive surgery	0.569	[-0.714,1.852]	0.385
ASA class (Ref: ASA>=3)			
ASA<=2	-1.105	[-2.106, -0.105]	0.030*
Anxiety diagnosis (Ref: Yes)			
No	0.029	[-0.782,0.841]	0.944
Neoadjuvant chemotherapy (Ref: Yes)			
No	0.669	[-0.910,2.248]	0.407
Preoperative opioid use (Ref: Yes)			
No	-0.319	[-1.115,0.476]	0.431
Preoperative pelvic pain (Ref: Yes)			
No	0.252	[-0.557,1.061]	0.541
Trajectory group (Ref: Ongoing pain)			
Rapid Resolution	-1.061	[-2.079, -0.042]	0.041*
Slow Resolution	-1.974	[-3.454, -0.502]	0.009**

Likelihood Ratio Chi-Square for the overall model is 23.154 with p=0.017.

Supplementary table5-GLM for Prolonged opioid use at 7 days after surgery (Ref: No)

	B	95% Wald Confidence Interval	p
Age	0.030	[-0.030, 0.090]	0.327
BMI	0.001	[-0.069, 0.061]	0.962
Diagnosis (Ref: Ovarian/ Fallopian tubal/Peritoneal cancer)			
Endometrial cancer	-1.212	[-0.118, 1.709]	0.108
Procedure (Ref: Total abdominal hysterectomy)			
Minimally invasive surgery	0.029	[-2.505,2.562]	0.982
ASA class (Ref: ASA>=3)			
ASA<=2	-1.704	[-3.915, -0.506]	0.131
Anxiety diagnosis (Ref: Yes)			
No	0.423	[-0.861,1.707]	0.518
Neoadjuvant chemotherapy (Ref: Yes)			
No	0.818	[-0.908,2.544]	0.353
Preoperative opioid use (Ref: Yes)			
No	0.814	[-0.386,2.014]	0.184
Preoperative pelvic pain (Ref: Yes)			
No	-1.092	[-2.462,0.278]	0.118
Trajectory group (Ref: Ongoing pain)			
Rapid Resolution	-17.934	[-5596, -11174]	0.997
Slow Resolution	-21.277	[-10574, 10534]	0.998

Likelihood Ratio Chi-Square for the overall model is 59.942 with $p<0.001$.

Supplementary table6-GLM for Prolonged opioid use at 2 weeks after surgery (Ref: No)

	B	95% Wald Confidence Interval	p
Age	0.002	[-0.032, 0.036]	0.910
BMI	0.009	[-0.053, 0.035]	0.692
Diagnosis (Ref: Ovarian/ Fallopian tubal/Peritoneal cancer)			
Endometrial cancer	0.432	[-0.478, 1.343]	0.352
Procedure (Ref: Total abdominal hysterectomy)			
Minimally invasive surgery	-1.077	[-2.627,0.473]	0.173
ASA class (Ref: ASA>=3)			
ASA<=2	0.061	[-0.727, 0.849]	0.879
Anxiety diagnosis (Ref: Yes)			
No	-0.150	[-0.957,0.657]	0.715
Neoadjuvant chemotherapy (Ref: Yes)			
No	0.202	[-1.141,1.544]	0.769
Preoperative opioid use (Ref: Yes)			
No	0.577	[-0.267,1.420]	0.180
Preoperative pelvic pain (Ref: Yes)			
No	-0.622	[-1.397,0.153]	0.116
Trajectory group (Ref: Ongoing pain)			
Rapid Resolution	-0.865	[-1.915, 0.185]	0.106
Slow Resolution	-0.248	[-1.385, 1.881]	0.766

Likelihood Ratio Chi-Square for the overall model is 12.529 with p=0.325.

Supplementary table7-GLM for Prolonged opioid use at 2 months after surgery (Ref: No)

	B	95% Wald Confidence Interval	p
Age	-0.039	[-0.082, 0.004]	0.073
BMI	-0.048	[-0.114, 0.018]	0.157
Diagnosis (Ref: Ovarian/ Fallopian tubal/Peritoneal cancer)			
Endometrial cancer	0.376	[-0.723, 1.474]	0.503
Procedure (Ref: Total abdominal hysterectomy)			
Minimally invasive surgery	-0.425	[-2.301,1.451]	0.657
ASA class (Ref: ASA>=3)			
ASA<=2	0.000	[-1.041, 1.042]	1.000
Anxiety diagnosis (Ref: Yes)			
No	-0.271	[-1.306,0.765]	0.608
Neoadjuvant chemotherapy (Ref: Yes)			
No	1.089	[-1.038,3.217]	0.316
Preoperative opioid use (Ref: Yes)			
No	0.815	[-0.283,1.913]	0.146
Preoperative pelvic pain (Ref: Yes)			
No	-0.141	[-1.172,0.890]	0.788
Trajectory group (Ref: Ongoing pain)			
Rapid Resolution	-0.962	[-2.217, 0.294]	0.133
Slow Resolution	-0.992	[-3.059, 1.075]	0.347

Likelihood Ratio Chi-Square for the overall model is 13,471 with p=0.264.

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