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Risk factors for persistent post surgical pain (PPSP): a systematic review and meta-analysis

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Thesis

**RISK FACTORS FOR PERSISTENT POSTSURGICAL PAIN (PPSP): A
SYSTEMATIC REVIEW AND META-ANALYSIS**

by

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PREMAL P PATEL

ABSTRACT

Persistent postsurgical pain (PPSP) is reported as recurrent and frequently disabling complication of many surgical procedures. The consequences for PPSP not only reduce the quality of life for patients but also financially tax the health care system, considering the volume of surgical procedures performed annually. Development of chronic pain has been proposed to involve a complex pathophysiology combined with pre-, intra-, and post-operative risk factors. There is no definite recommendation on which factor to assess (in which surgery) and what tools to utilize for conducting a study on PPSP, since many recognized risk factors for PPSP are contradictory. For a comprehensive overview of major PPSP risk factors for identification and possible prevention, we conducted a systematic review and meta-analysis of the published literature on the risk factors across six major surgical groups: breast surgery, chest/thoracic surgery, total hip arthroplasty/total knee arthroplasty (THA/TKA), gynecologic surgery, iliac crest bone harvest (ICBH), and groin hernia repair. Furthermore, to assess the generalizability of the meta-analysis results, we sought to conduct a retrospective, cross-sectional study examining the prevalence and major risk factors of PPSP after cystectomy for bladder cancer. The meta-analysis found that no single risk factor was associated with

PPSP across all surgical groups. Age and previous surgery were found to be risk factors for PPSP in gynecologic surgery. For thoracic surgery, male sex and BMI were found as risk factors for PPSP. Surgical duration, presurgical chronic pain, and BMI were risk factors for groin hernia repair. The prevalence of PPSP in our cystectomy study was 22.1%. Female sex and presurgical chronic pain were risk factors significantly associated with PPSP after cystectomy. No risk factors were universally associated with PPSP. Persistent pain after each type of surgical procedure appear to have separate set risk factors among age, BMI, sex, previous surgery, and presurgical pain.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CPSP	Chronic postsurgical pain
CSQ	Coping Strategies Questionnaire
HADS	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
ICBH	Iliac Crest Bone Harvest
PCS	Pain catastrophizing scale
PPMCC	Pearson's momentum correlation coefficient
PPSP	Persistent Post-surgical pain
STAI	State-Trait Anxiety Inventory
THA	Total hip arthroplasty
TKA	Total knee arthroplasty

INTRODUCTION

Acute pain and inflammation arising from tissue damage following surgical interventions are anticipated physiological responses. Generally, the postsurgical pain resolves once the damaged tissue heals. However, some patients undergoing common surgical procedures report varying degrees of pain long after surgery. The incidence of this persistent postsurgical pain (PPSP), also referred to as chronic postsurgical pain (CPSP), varies from operation to operation and between studies. Additionally, there is no standardized definition for PPSP. Considering 318 million surgical procedures performed annually around the world, the consequences for chronic postsurgical pain not only include reduced quality of life for the patient but also a substantial fiscal burden to the health care system (Blyth, March, & Cousins, 2003; Shrima, Daniels, & Meara, 2015).

Definition of PPSP

The most commonly used description for PPSP comes from Macrae and Davis (Macrae, 2008). They proposed the following specific criteria for postsurgical pain to be considered chronic: (i) the pain develops after a surgical procedure, (ii) the pain is of at least two months duration, (iii) other cause for the pain should have been excluded, (iv) the possibility that the pain is continuing from a pre-existing problem has been excluded (Macrae, 2008). The proposed criteria are comparable to the International Association for the Study of Pain

(IASP) definition for chronic pain. However, the time frame of two months has been questioned due to ongoing inflammatory processes lasting more than two months (Kehlet & Rathmell, 2010). The assumption under these criteria is that acute postoperative pain evolves into chronic pain.

Epidemiology

Depending on the definitions, estimates on incidence vary widely, but overall between 10 and 50% of surgical patients report some degree of persistent pain at 3-6 months postoperatively (Kehlet, Jensen, & Woolf, 2006). Table 1 provides a sample of reported incidences of persistent postoperative pain after a variety of surgical procedures (Haroutiunian, Nikolajsen, Finnerup, & Jensen, 2013). The sizable variability in reported PPSP can be attributed to many factors, including demographics, preoperative patient characteristics, surgical techniques, and perioperative analgesia regimens. However, discrepancies in the definition and methodology of assessment of PPSP provide the largest variation.

In general, estimates of PPSP are determined from retrospective cross-sectional studies, clinical trials, and prospective surgical cohorts. Most studies of PPSP have focused on the type of the surgical procedure, including thoracotomy, breast surgery, total hip arthroplasty/total knee arthroplasty (THA/TKA), iliac crest bone harvest (ICBH), and abdominal surgery. There is some evidence to suggest higher rates of PPSP after certain surgeries. On the other hand, for certain surgical procedures such as cystectomy for bladder cancer, data are lacking.

A variety of methodological, demographic and surgical factors contribute to the large variability in the estimates of PPSP epidemiology. Standardized study methodology is unlikely to result in consistent PPSP incidence rates because of the abundant factors affecting PPSP (Niraj & Rowbotham, 2011); however, by standardizing PPSP assessment, it is likely that a potential strategy can be determined for identifying individual risk factors for PPSP development.

Table 1. Prevalence of PPSP as reported. The median and IQR of PPSP prevalence based on conservative and liberal criteria for calculation. A single point prevalence of PPSP was extracted for each study (Table adapted from (Haroutiunian *et al.*, 2013)).

Surgery type	No. of studies used in PPSP prevalence calculation	Sample size, median no. of patients (range)	Time from surgery to pain assessment	PPSP prevalence %, conservative approach (median, IQR)	PPSP prevalence %, liberal approach (median, IQR)
Thoracic surgery	44	86 (23–1080)	2 mo–12 y	34.5 (21–52)	37 (23.5–52)
Breast surgery	53	106 (22–3253)	2 mo–35 y	31 (21.5–47.3)	41 (24.3–49)
Abdominal surgery	6	86 (22–286)	1–10 y	11 (4.7–18)	11.5 (3.5–18)
Donor nephrectomy	12	75 (53–359)	1.5 mo–15 y	9.6 (3.2–25)	21.3 (3.7–33)
Gynecologic surgery	13	90 (36–1135)	3–24 mo	13.7 (7.8–17.3)	17 (11.5–34.5)
Prostatectomy	8	95 (24–179)	2.5–6 mo	14 (8–36)	21 (10.4–36)
Groin hernia repair	89	266 (22–5524)	1.5 mo–12 y	7 (2.5–19)	12 (4.4–23.6)
THA/TKA	13	142 (20–7230)	4 mo–8 y	19.8 (11.7–27.7)	27 (12.5–39.1)
Iliac crest bone harvest	29	94.5 (10–414)	3 mo–13 y	18.7 (12.5–28.3)	23.5 (14.7–35.1)
Mandibular osteotomy	1	20	12 mo	10	10
Varicose vein surgery	6	83.5 (35–126)	3 mo–11 y	4.7 (4–13)	4.7 (4–13)

Risk Factors

To prevent a condition, it would be of interest to understand the root causes and identify the predictors for its occurrence. Unfortunately, there is debate on the underlying mechanisms of PPSP (Macrae, 2008). Nevertheless, there has been significant contribution in identifying putative risk factors that contribute to the development of PPSP.

Age

Although not consistent across all studies, younger patients seem to be more likely to develop PPSP. For breast cancer surgery, it was shown that the frequency of PPSP decreased with age (Andersen & Kehlet, 2011). Similar associations with younger age were seen with inguinal hernia repairs and cardiac surgery (Gjeilo, Klepstad, Wahba, Lydersen, & Stenseth, 2010; Poobalan *et al.*, 2001).

Presurgical pain

Presurgical pain at or near the operative site has been found to predict chronic pain. Moderate to intense presurgical pain has been associated with the presence of chronic pain lasting >6 months for abdominal surgery (OR 1.75; 95% CI 1.32–2.19) (Caumo *et al.*, 2002). Presurgical pain was the most significant clinical predictive factor associated with greater odds of PPSP development for patients undergoing THA/TKA (Pinto, McIntyre, Ferrero, Almeida, & Araújo-Soares, 2013). In a prospective study, it was found that the presence of pain

prior to surgery resulted in a sevenfold higher risk of pain at the 12-month follow-up for patients undergoing thoracotomy (Hetmann, Kongsgaard, Sandvik, & Schou-Bredal, 2015).

Psychological Factors

Early studies investigating PPSP primarily focused on demographic and perioperative factors, however there has been recent interest and findings in the role of psychological factors predicting surgical pain outcomes (Bruce & Quinlan, 2011).

Preoperative depression had an increased association with PPSP after knee arthroplasty and breast surgery (Masselin-Dubois *et al.*, 2013; Sipilä, Estlander, Tasmuth, Kataja, & Kalso, 2012).

Preoperative anxiety was found to be predictive of acute postoperative pain for patients undergoing abdominal surgery (Caumo *et al.*, 2002).

Additionally, anxiety correlated with PPSP after knee and hip arthroplasty (Pinto *et al.*, 2013).

Lastly, catastrophizing (defined as “a negative cognitive and affective response to pain”) has been shown to influence pain-related outcomes (Edwards, Bingham, Bathon, & Haythornthwaite, 2006). Presurgical catastrophizing has been reported as one of the most important predictors of pain after TKA and THA (Faller, Kirschner, & König, 2003; Forsythe, Dunbar, Hennigar, Sullivan, & Gross; Sullivan *et al.*, 2011).

Reoperation

The number of previous operations was one of the variables predicting PPSP after breast cancer surgery. It was hypothesized that several operations could have sensitized the central nervous system or the need for multiple operations is related to greater chronic diseases and systemic inflammation causing more chronic pain and sensitization of the pain system (Sipilä, Estlander, Tasmuth, Kataja, & Kalso, 2012).

Other Factors

Genetic factors may also be implicated as a risk factor for the development of pain. More specifically catecholamine-O-methyltransferase (COMT) activity correlates with the increased development chronic temporomandibular joint pain (Kehlet *et al.*, 2006).

There is evidence that anesthetic and analgesic regimens may be instrumental in reducing the development of chronic pain. Some studies indicate the regional anesthesia for ICBH (Gündeş, Kiliçkan, Gürkan, Sarlak, & Toker, 2000) and thoracic surgery (Senturk *et al.*, 2002) reduce the risk of PPSP.

BMI is another risk factor that may be associated with PPSP. Studies regarding THA and groin hernia repair associate higher BMI with an increased risk for chronic pain development (Berrevoet, Vanlander, Bontinck, & Troisi, 2013; Busato, Röder, Herren, & Eggli, 2008).

SPECIFIC AIMS

With PPSP being a potentially preventable condition, there is a need to understand the individual risk factors leading and/or contributing to its development. Understanding these factors can serve as a basis for investigating approaches for risk stratification and prevention of PPSP. With many putative risk factors for PPSP being contradictory, there is no definite recommendation on which factors to assess for different types of surgeries, and what tools to utilize for conducting a comprehensive study on PPSP.

The objective of this thesis is to investigate and provide an updated meta-analysis on major risk factors for PPSP and a better understanding and possible prevention of this condition.

To meet the research objectives, we conducted two sub-studies:

- (1) We conducted a systematic review and meta-analysis of the published literature on the risk factors across six major surgical groups: breast surgeries, chest/thoracic surgeries, gynecological surgeries, TKA/THA, hernia, and ICHB surgeries.
- (2) Additionally, to independently examine the generalizability of the meta-analysis results, we sought to determine the prevalence and major risk factors of PPSP after cystectomy for bladder cancer by conducting a cross-sectional survey study. Bladder cancer is the fourth most commonly diagnosed malignancy in the United States; more than 72,000 Americans are estimated to be diagnosed with bladder cancer and

approximately 15,000 patients a year predicted to die of bladder cancer (Kaufman, Shipley, & Feldman, 2009). No data are currently available on the prevalence of PPSP after cystectomy, therefore, we chose it as an appropriate surgical procedure for this sub-study 2.

Based on the prevalence of PPSP after other surgeries requiring a lower abdominal incision such as prostatectomy and hysterectomy, at 9.6-14%, we expect that 10-15 % of patients undergoing cystectomy will develop PPSP (Haroutiunian *et al.*, 2013).

METHODS

Study 1 – Systematic review and meta-analysis

Search Strategy

Studies assessing the occurrence and characteristics of pain after the following nine surgical procedures were searched: (i) breast surgery (ii) chest/thoracic surgery (iii) gynecologic surgery (hysterectomy and cesarean section), (iv) groin hernia repair, (v) total hip arthroplasty/total knee arthroplasty (THA/TKA), (vi) iliac crest bone harvest (ICBH), (vii) nephrectomy, (viii) prostatectomy, and (ix) abdominal surgery. However, only the first 6 surgical procedures were used for this study. MEDLINE (PubMed), EMBASE, and Cochrane CENTRAL databases were first searched in January 2012 followed with a search update in October 2014 that included the following search keywords: Mesh terms “Pain, Postoperative” and “Surgical Procedures, Operative” with “chronic pain” or “long term pain” keywords (“postoperative pain” and “surgery” with “chronic pain” in EMBASE).

Furthermore, “Pain, postoperative”[Mesh] term was combined in a separate MEDLINE search with one of the following: “Thoracic surgical procedures”[Mesh], “Mammoplasty”[Mesh], “Mastectomy, Segmental”[Mesh], “Abdomen/surgery”[Mesh], “Nephrectomy”[Mesh], “Hysterectomy”[Mesh], “Cesarean section”[Mesh], “Prostatectomy”[Mesh], “Hernia, Inguinal/surgery”[Mesh], “Arthroplasty, Replacement, Hip”[Mesh], “Arthroplasty, replacement, knee”[Mesh], “Ilium/surgery”[Mesh], “Mandible/surgery”[Mesh] or

“Varicose veins/surgery”[Mesh]. Additional articles were retrieved from the references of the identified studies and from reviews on the topic.

Study Selection

Inclusion Criteria

The identified abstracts/titles were screened independently by two researchers to meet the following inclusion criteria:

(1) Studies considered eligible for inclusion within the meta-analysis belonged to the following 6 surgical procedures: (i) breast surgery (ii) chest/thoracic surgery (iii) gynecologic surgery (hysterectomy and cesarean section), (iv) groin hernia repair, (v) total hip arthroplasty/total knee arthroplasty (THA/TKA), and (vi) iliac crest bone harvest;

(2) Provided definition of PPSP as primary/secondary outcome or specifically described in methods as one of the study objectives and reported occurrence of PPSP;

(3) Studies published after 1979 were considered.

Exclusion Criteria

The studies were excluded if they met any of the following 5 criteria:

(1) Studies which did not include subject undergoing (i) breast surgery (ii) chest/thoracic surgery (iii) gynecologic surgery (hysterectomy and cesarean section), (iv) groin hernia repair, (v) total hip arthroplasty/total knee arthroplasty (THA/TKA), and (vi) iliac crest bone harvest (ICBH);

(2) Studies with follow-up of less than 2 months (studies in which less than 10% of patients had a follow-up between 1-2 months were included);

(3) studies including patients younger than 13 years old;

(4) studies on patients with established PPSP that did not report the occurrence of persistent pain;

(5) abstracts and studies/case reports including less than 10 patients per arm.

Potential Bias Assessment

Three categories were assessed for descriptive information regarding potential risk of bias: (i) the sample adequately represents the population of interest, (ii) the data represent the sample, and (iii) the outcome of interest (chronic pain) is adequately measured to limit potential bias. Within each category, three queries regarding the studies assessed were answered with: Yes, No, or Unclear. Lastly, based on the responses an overall grading was selected. APPENDIX A represents the extraction form which includes descriptive for potential sources of bias assessment and the methodology for providing an overall grading.

Data Extraction

Extracted data of the selected studies were tabulated into a text extraction form (APPENDIX A) reporting the following data:

- Author, Title, Journal, Year, Funding source

- Type of surgery (e.g. thoracic, TKA), indication for surgery (e.g. cancer, osteoarthritis) and surgical approach (e.g. open, laparoscopic, VATS)
- Study design: prospective vs retrospective,
- Control groups: Uncontrolled = single group, Controlled = included 2 or more groups
- Study type: interventional, cohort, chart review, survey etc...
- Single-center or multicenter
- Length of follow-up (record each follow-up at which PPSP was assessed and reported)
- Definition of PPSP in the study (e.g. any pain at the time of interview; pain in the surgical scar for at least X weeks duration, with intensity >3)
- Pain intensity cut-off to be considered PPSP, if exists.
- Relevant exclusion criteria (preexisting pain, anxiety etc.)
- No. of participants enrolled
- No of participants at each of the relevant follow-ups (per arm, if several arms)
- No of patients with PPSP at each of the relevant follow-ups. In case of liberal and conservative estimates are reported (e.g. # with any pain or discomfort vs # with moderate to severe pain), the conservative (moderate to severe pain) was included.

Additionally, APPENDIX A. provides the parameters what were extracted as potential risk factors regardless if the study had assessed its association with PPSP.

Data analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Washington University School of Medicine (Harris *et al.*, 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: (i) an intuitive interface for validated data entry; (ii) audit trails for tracking data manipulation and export procedures; (iii) automated export procedures for seamless data downloads to common statistical packages; and (iv) procedures for importing data from external sources.

Analyses were conducted using SPSS Statistics 23.0. Each study arm was treated as an individual case. Descriptive statistics were used to show the number of different outcome measures that assessed pain and assess the normality of the PPSP ratio. The primary outcome, PPSP ratio, was calculated by the number of subject reporting PPSP as defined by the study out of the overall number of subjects assessed at follow up. The data were normalized with the square root function if the outcome data were not normally distributed. The outcomes were categorized into 3 groups: PPSP at first follow-up, PPSP at follow-ups less than 6 months, and PPSP at follow ups equal to or greater than 6 months (e.g., a study with two follow-ups at 2 and 8 months would have a PPSP

ratio for all 3 groups). Risk factors that were exclusion criteria for patients in the study were removed from analysis and measures were normalized to a single scale. For each surgical group and overall group, bivariate Pearson correlations were carried out. Significant risk factors were entered in a regression model in a stepwise method. For all stages of data analyses, the significant level was $p < 0.05$.

Study 2 - Cross-sectional Survey

The study to determine the prevalence and risk factors associated with PPSP following cystectomy was approved by the IRB at Washington University in St. Louis (IRB #201509131). Patients over 18 years of age who had undergone cystectomy for bladder cancer between Jan 1, 2009 to Nov 30, 2015 at Washington University/Barnes-Jewish Hospital were considered for participation in the survey.

Patient Selection

Inclusion Criteria

The inclusion criteria included the following:

(1) Patient was at least 18 years old and the cystectomy for bladder cancer was performed at Washington University/Barnes-Jewish Hospital between Jan 1, 2009 and Nov 30, 2015.

Exclusion Criteria

The exclusion criteria included the following:

(1) Patient was deceased;

(2) Patient moved out of the United States;

(3) Patient's preoperative record indicated 2 or more surgeries in the abdominopelvic region.

Contact Protocol

An introductory letter notifying the patients of an upcoming survey and its objective was mailed to all subjects. One week later, a postal survey with a pre-stamped return envelope was sent. The survey (APPENDIX B) included questions on the presence of PPSP, its intensity, duration, characteristics and effect on functioning and quality of life. The survey also included a written agreement to be contacted for participation in the quantitative sensory testing (QST) examination session at the Department of Anesthesiology at Washington University.

Preoperative, Intraoperative and Postoperative Data and Complications

Standard preoperative evaluation data that includes a detailed medical history and evaluation of preoperative functional status containing preoperative pain scores, history of persistent pain and preoperative analgesic were collected from ClinDesk (a Java-based electronic patient record database) and Metavision Database at the Department of Anesthesiology at Washington University/Barnes-Jewish Hospital.

Data Analysis

Study data was collected and stored with REDCap. Analyses were conducted using SPSS Statistics 23.0. The primary outcome was calculated as the percentage of subjects that reported PPSP among the survey responders. Comparison of nominal variables was performed by Fisher's exact test ($p < 0.05$) and comparison of continuous variables was performed by Student's *t* test ($p < 0.05$).

RESULTS

Study 1 – Systematic review and meta-analysis

Literature search and Study Characteristics

The total number of articles identified by the literature search from PubMed, CENTRAL, and Embase was 6650. These articles were skimmed by titles/abstracts, and 368 potential articles were identified to extract. Thirty-nine studies regarding abdominal surgery, nephrectomy, prostatectomy, and mixed surgeries were outside the scope of this thesis, therefore were not included in the analyses. The full texts of the relevant articles was evaluated for the inclusion criterion and extracted for data by two researchers independently. Each article extraction was verified for accuracy and conflicting interpretations were resolved by discussion among the research team. Application of the exclusion criterion resulted in the final number of 275 articles for this systematic review. Figure 1 is a flowchart of the literature search and study selection. Each arm of these studies being considered an independent case, there were a total of 399 individual cases.

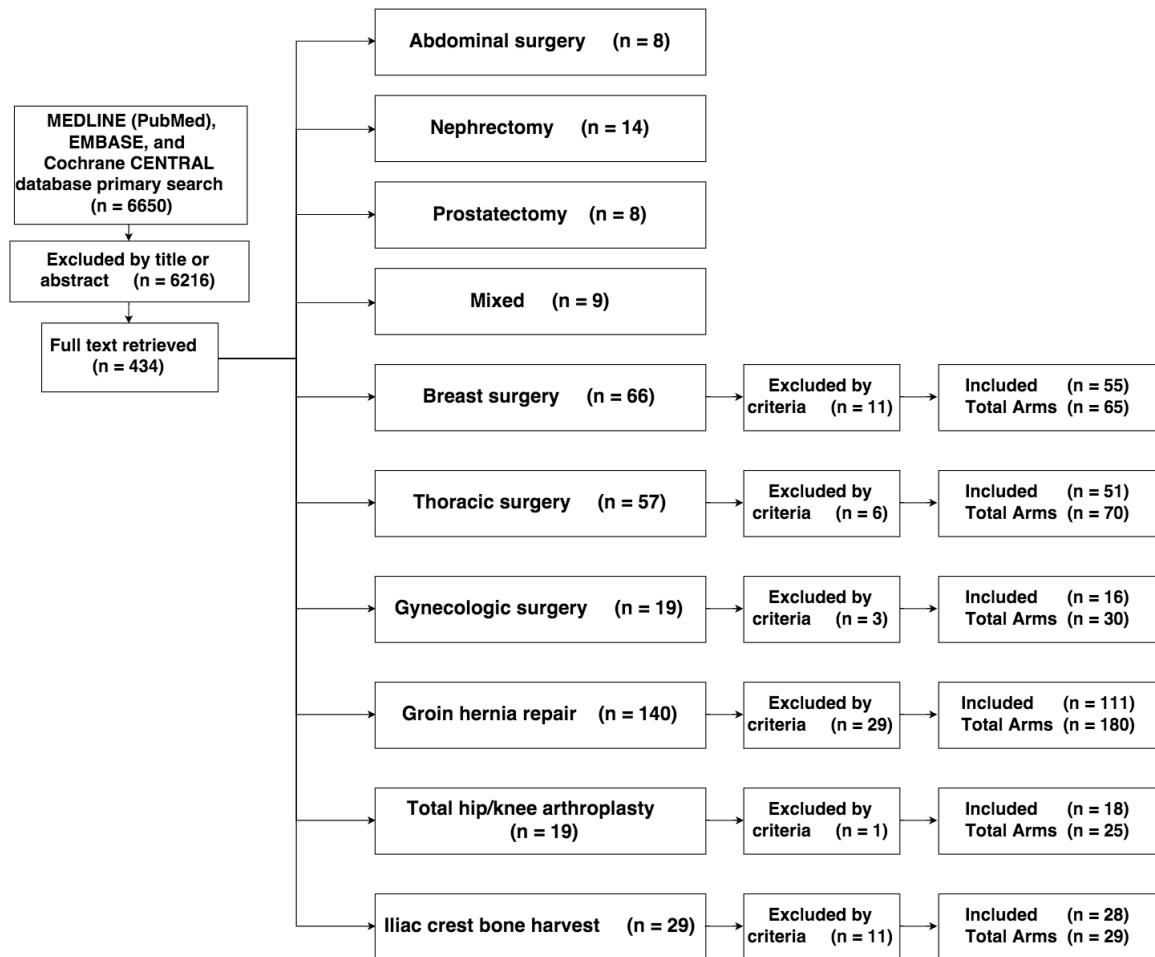


Figure 1. Literature search and study selection flowchart. Articles for the meta-analysis and systematic review were identified from a literature search then selected based on inclusion criteria factors.

Characteristics of Included Surgery Types

Within each surgery groups, types of surgical procedures were examined.

Breast surgery included mastectomy (radical or modified) without axillary lymph node dissection, mastectomy (radical or modified) with axillary lymph node dissection, lumpectomy or breast-conserving surgery, biopsy, breast

augmentation, and breast reduction. Thoracic surgery included thoracotomy, mini-thoracotomy, video-assisted thoracoscopy (VATS), sternotomy, and sternothoracotomy. THA/TKA section included THA both open-minimally invasive, and TKA both open-minimally invasive. Gynecological surgeries included cesarean section, open hysterectomy, laparoscopic hysterectomy, and vaginal hysterectomy. Iliac crest bone harvest included posterior and anterior ICBH. Groin hernia repair included mesh and without mesh open and laparoscopic or endoscopic. For each surgery group, few studies did not report the surgical approach. Furthermore, additional surgical procedures were listed for some of the surgery groups.

The risk bias was addressed and 16.7% of a studies evaluated presented at least some potential bias categorized as unclear or unknown. The majority of the studies presented potential bias regarding the data representing the sample. Table 2 reports the frequency of the potential sources of bias assessment.

Table 2. Frequency of potential sources of bias assessment. Articles that were selected from the meta-analysis and systematic review were assessed for bias based on a formulated methodology.

Potential sources of bias assessment:	Frequency (%)	
I. The sample adequately represents the population of interest	Yes	71.2
	Partly	24.6
	Unclear	3.6
	No	0.4
II. The data represent the sample	Yes	52.5
	Partly	39.3
	Unclear	8.1
	No	1.1
III. The outcome of interest (chronic pain) is adequately measured to limit potential bias.	Yes	59.9
	Partly	31.0
	Unclear	5.0

Prevalence of PPSP

The highest mean prevalence of PPSP at first follow-up was found after thoracic and breast surgeries (36.8% and 34.7%). This was followed by the prevalence of THA/TKA and gynecological surgeries (27.4% and 21.1%). The lowest prevalence of PPSP of the 6 surgical groups was found in iliac crest bone and groin hernia repair (20.0% and 14.3%). Descriptive statistics including median and IQR of PPSP prevalence rates for the studies included in the systematic review are summarized in Table 3. Figure 2 displays the large spread of reported PPSP at first follow ups across all surgical groups examined.

Table 3. Prevalence of PPSP for present study. The median and IQR for the PPSP prevalence at first follow-ups, follow-ups less than 6 months, and follows ups greater than or equal to 6 months for the number of studies within each group are presented.

Surgery type	No. of studies used in PPSP prevalence calculation	PPSP at first follow up % (median, IQR)	PPSP at follow up < 6months %, (median, IQR)	PPSP at follow up ≥ 6 months %, (median, IQR)
All surgical cases	275	20 (8-34)	20 (10-45)	17 (6-30)
Breast surgery	55	33 (17-45)	47 (29-64)	29 (17-40)
Thoracic surgery	50	34 (20-52)	35 (19-63)	31 (20-50)
THA/TKA	18	27 (14-37)	20 (11-30)	27 (13-37)
Gynecologic surgery	16	11 (18-30)	17 (08-20)	17 (7.5-32)
Groin hernia repair	117	11 (3.0-23)	11 (5.0-28)	11 (3.0-21)
Iliac crest bone harvest	19	18 (11-27)	18 (11-34)	20 (11-28)

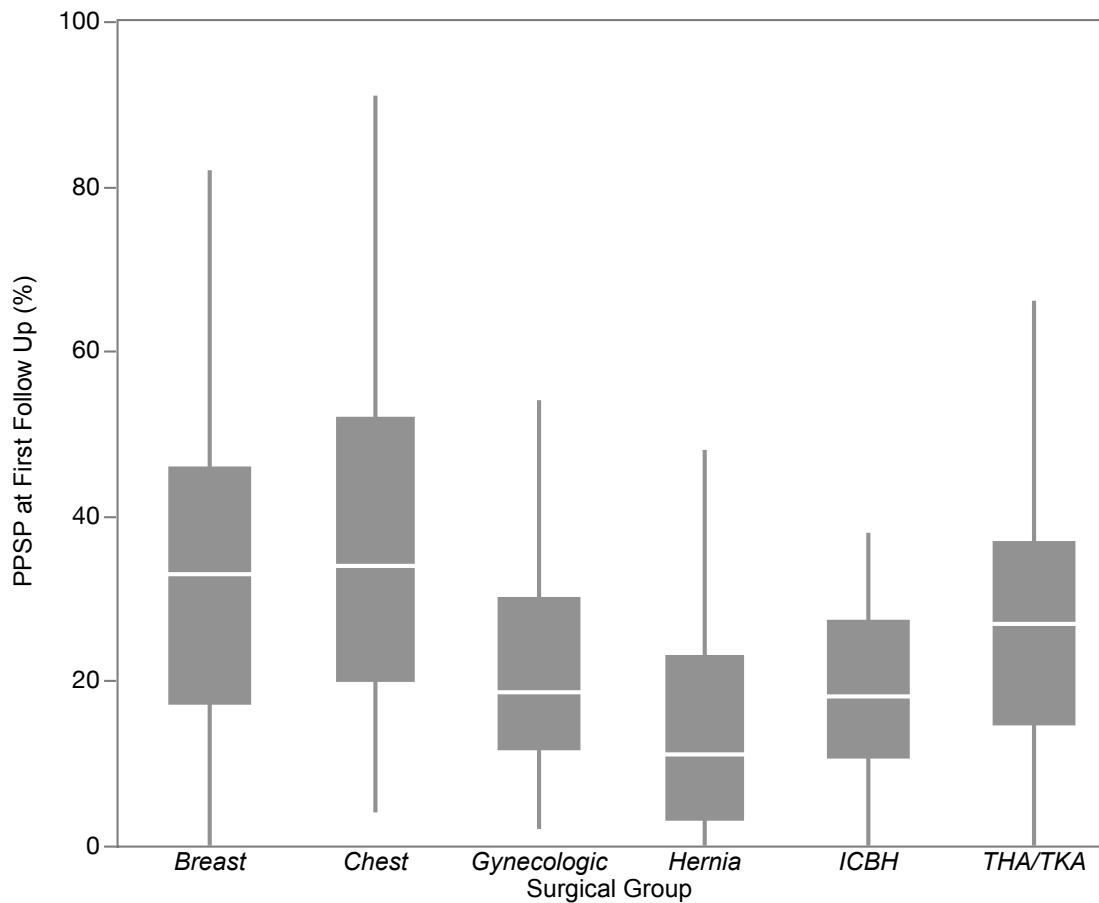


Figure 2. Box Plot for Prevalence of PPSP of Present Study. Prevalence rate of PPSP grouped by surgical type for the articles considered for the meta-analysis and systematic review.

All Surgical Types

Of the 368 articles identified for PPSP, 275 articles were included in the final analysis with a total of 399 arms. For this study, arms were not combined as merging individual case for the studies resulted in the omission of risk factors

assessed in the studies. APPENDIX C displays the reporting frequency of all variables.

Bivariate Analysis for All Surgical Types

Since total data was negatively skewed because the majority of the arms in this meta-analysis came from the groin hernia repair, the 3 outcomes groups were normalized before conducting a bivariate analysis. For the all surgical cases, only two risk factors were significant. PPSP prevalence was correlated to increase mean age (Pearson product-moment correlation coefficient [PPMCC]=0.247, $p=0.008$, $n=113$) and longer duration of surgery (PPMCC=0.313, $p=0.012$, $n=64$)

Regression for All Surgical Types

A multiple regression model with surgical duration and reported mean age for PPSP prevalence at follow ups less than 6 months was not significant ($F[2,52]=2.91$, $p=0.064$, $R^2=0.101$). Regression with only surgical duration was significant however the R^2 indicated that surgical duration explains only about 10% of the variability in PPSP ($F[1,62]=6.718$, $p=0.012$, $R^2=0.098$).

Breast Surgery

Of the 66 articles identified for PPSP after breast surgery, 11 articles were excluded based on the exclusion criteria (6 articles excluded on exclusion criterion 2, 1 article excluded on criterion 3, and 4 articles excluded on criterion 5). Of the included studies there were a total of 65 arms. APPENDIX C displays the reporting frequency of all variables for the breast surgery group.

Bivariate Analysis for Breast Surgery

Significant correlations were found between the percentage of smokers reported and prevalence of PPSP at first follow ups (PPMCC=0.807, $p=0.028$, $n=7$).

Additionally, two other correlations were found which did not involve PPSP rates. Mean age and mean BMI were positively correlated (PPMCC=0.647, $p=0.005$, $n=17$). Anxiety normalized to a single scale and surgery duration were also positively correlated (PMCC=0.986, $p=0.014$, $n=4$).

Regression for Breast Surgery

The relationship between PPSP and smoking was strongly associated. We conducted a single factor regression analysis for possible risk factor predictors of PPSP. Smoking status was a significant predictor for prevalence of PPSP in the regression analysis ($F[1,5]=9.347$, $p=0.028$, $R^2=0.651$). Based off the beta model, smoking increased the risk of PPSP development for patients undergoing breast surgery.

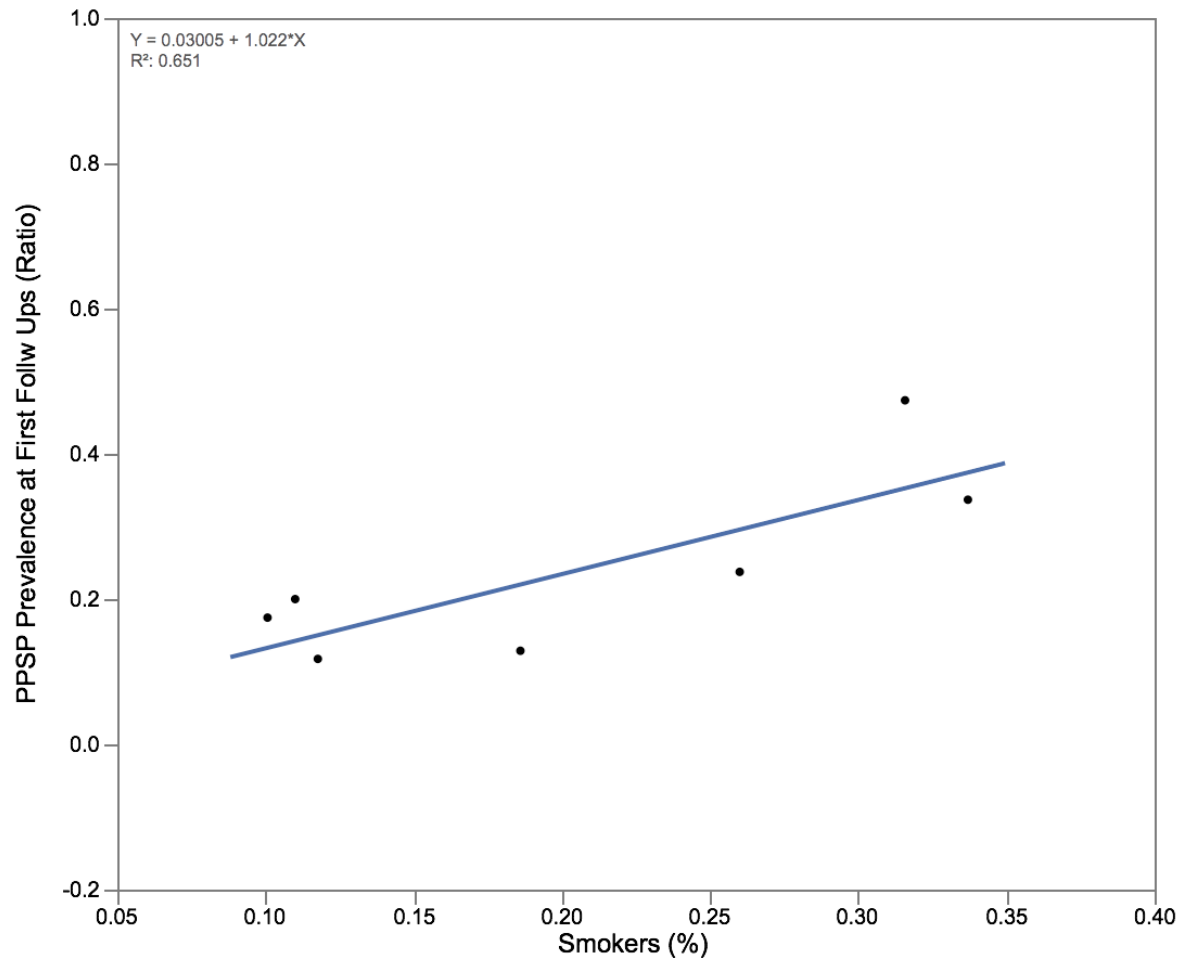


Figure 3. Scatter plot of PPSP prevalence at first follow ups vs smokers reported (%) for breast surgery. Positive linear relationship between PPSP at first follow ups and smoking status with linear equation.

Thoracic Surgery

55 articles were identified for PPSP after thoracic surgery of which 5 were excluded (2 articles excluded on exclusion criterion 3, 1 article excluded on criterion 4, 1 article excluded on criterion 5, and 1 article excluded on criterion 6). Of the included studies, there was a total of 70 arms. APPENDIX C displays the reporting frequency of all variables for the thoracic surgery group

Bivariate Analysis of Thoracic Surgery

There was a significant correlation between the prevalence of PPSP at follow ups ≥ 6 months for mean reported BMI and sex ratio (males/females) (PPMCC=-0.481, $p=0.037$, $n=19$; PPMCC=0.285, $p=0.039$, $n=53$) presented in Figure 4 and Figure 5.

Risk factors for PPSP were correlated. Mean age was positively correlated with BMI mean (PPMCC=0.638, $p<0.00$, $n=26$) and longer surgery duration was positively correlated with age mean (PPMCC=0.537, $p=0.005$, $n=26$).

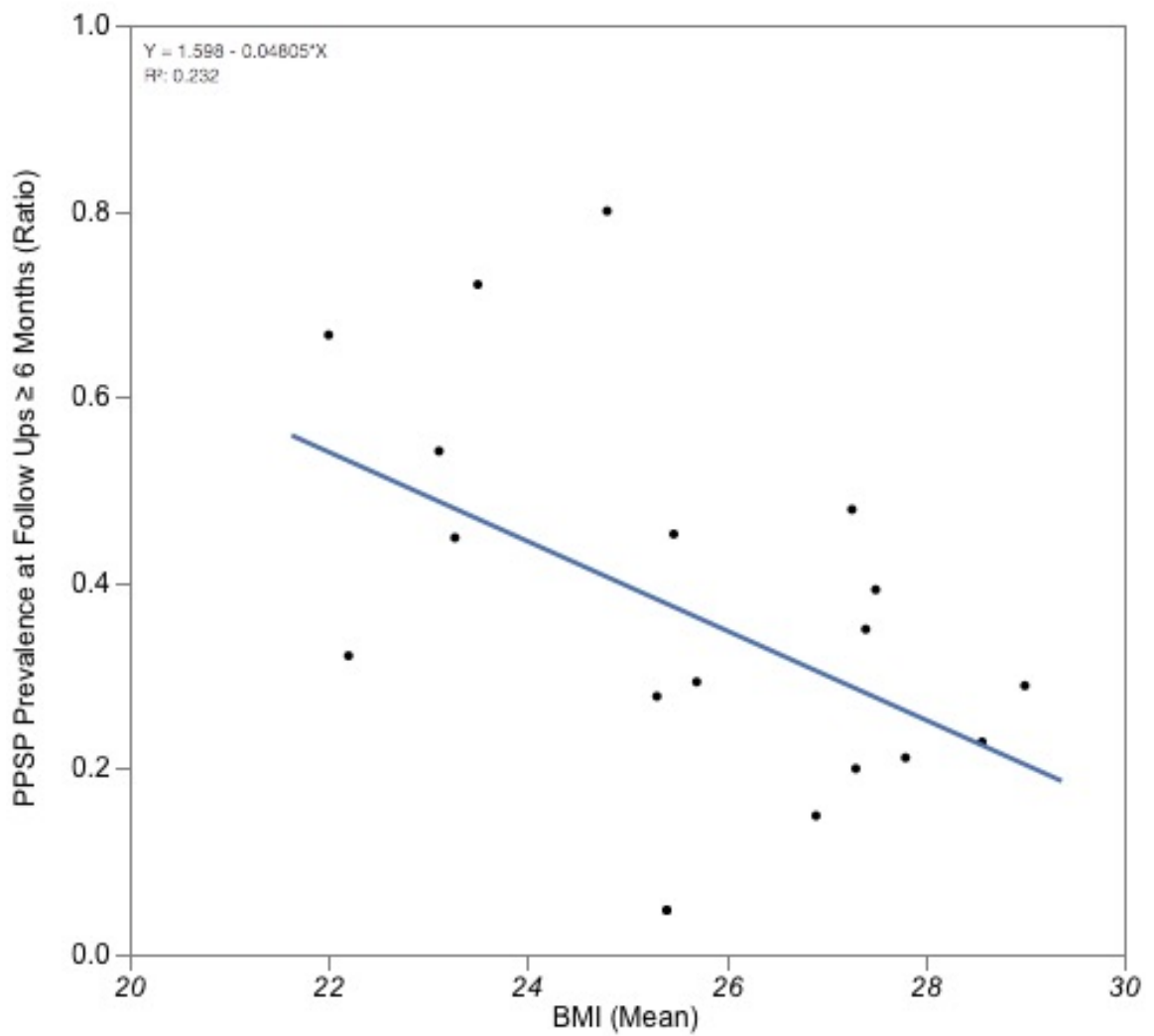


Figure 4. Scatter plot of PPSP prevalence at follow ups ≥ 6 months vs BMI (mean) for thoracic surgery. Negative linear relationship between PPSP at follow up greater than or equal to 6 months and BMI with linear equation.

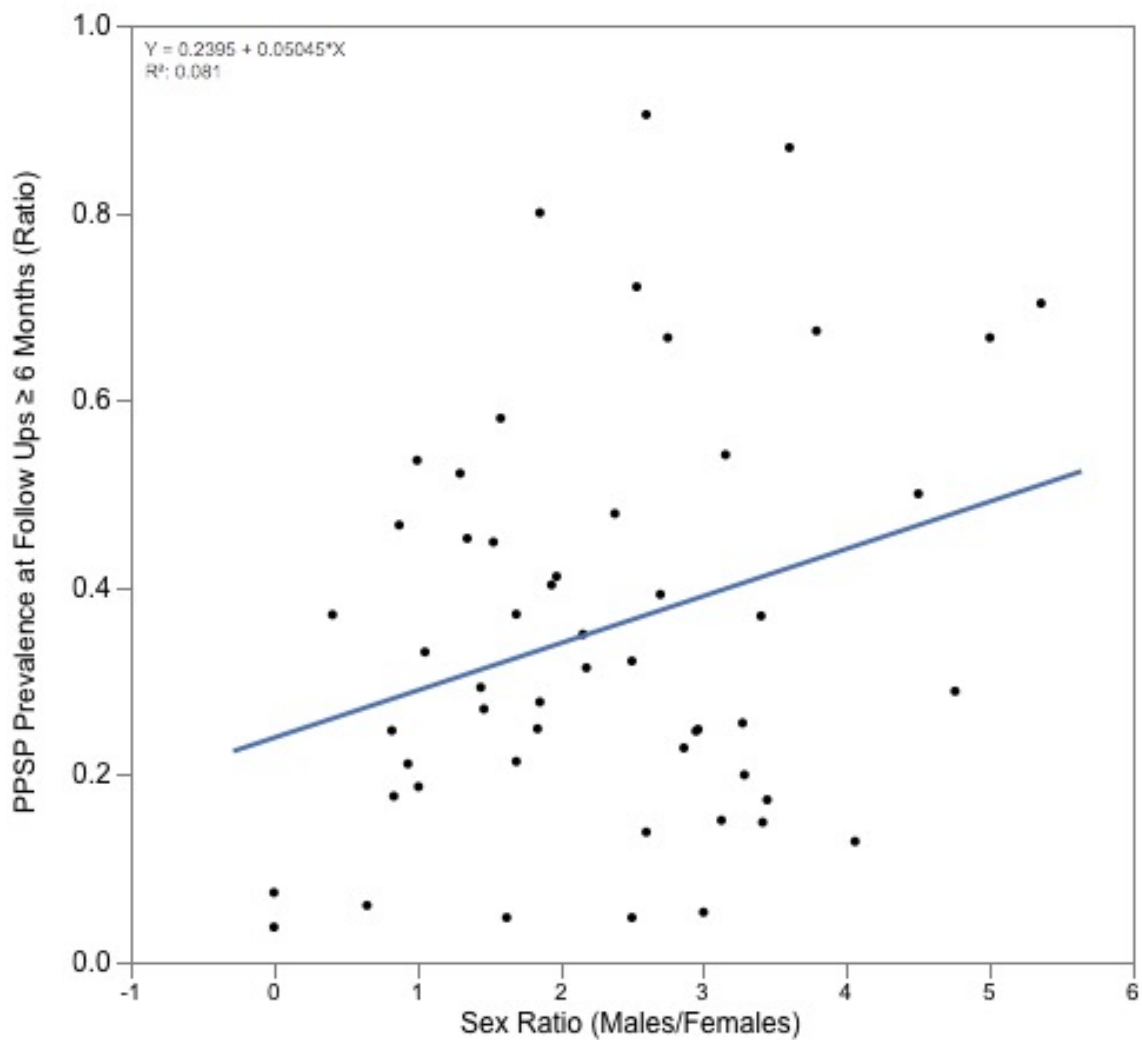


Figure 5. Scatter plot of the PPSP prevalence at follow ups \geq 6 months vs sex ratio (males/females) for thoracic surgery. Positive relationship of PPSP prevalence at follow ups greater than or equal to 6 month and sex ratio (males/female) with linear equation.

Regression for Thoracic Surgery

Based on the bivariate analysis that indicated a strong correlation between the prevalence of PPSP at follow-ups equal to or greater than 6 months and BMI mean, and sex ratio (males/female), an initial two factor regression model was

conducted. However, the observed significance level for sex ratio (males/females) indicated that this risk factor did not have statistically significant predictive capability ($p=0.076$). Removing sex ratio (males/females) and conducting a regression on BMI and PPSP prevalence at follow-ups ≥ 6 months showed statistical significance ($F[1,17]=5.15$, $p=0.037$, $R^2=0.232$). Based on the beta from the regression, lower BMI is predictive of higher PPSP prevalence.

THA/TKA Surgery

Of the 19 articles that were identified for PPSP after THA/TKA surgery, only 1 article was excluded on not fulfilling criterion 4 and 5. There were a total of 25 arms. APPENDIX C displays the reporting frequency of all variables for the THA/TKA surgery group.

Bivariate Analysis of THA/TKA Surgery

There was significant negative correlation between BMI mean and PPSP prevalence at follow ups ≥ 6 months ($PPMCC=-0.761$, $p=0.017$, $n=9$) as presented in Figure 6.

Two statically significant correlations were found between risk factors for PPSP. A negative correlation was found between the percentage of patients on preoperative opioids and sex ratio (female/male) ($PPMCC=-0.873$, $p=0.023$, $n=6$).

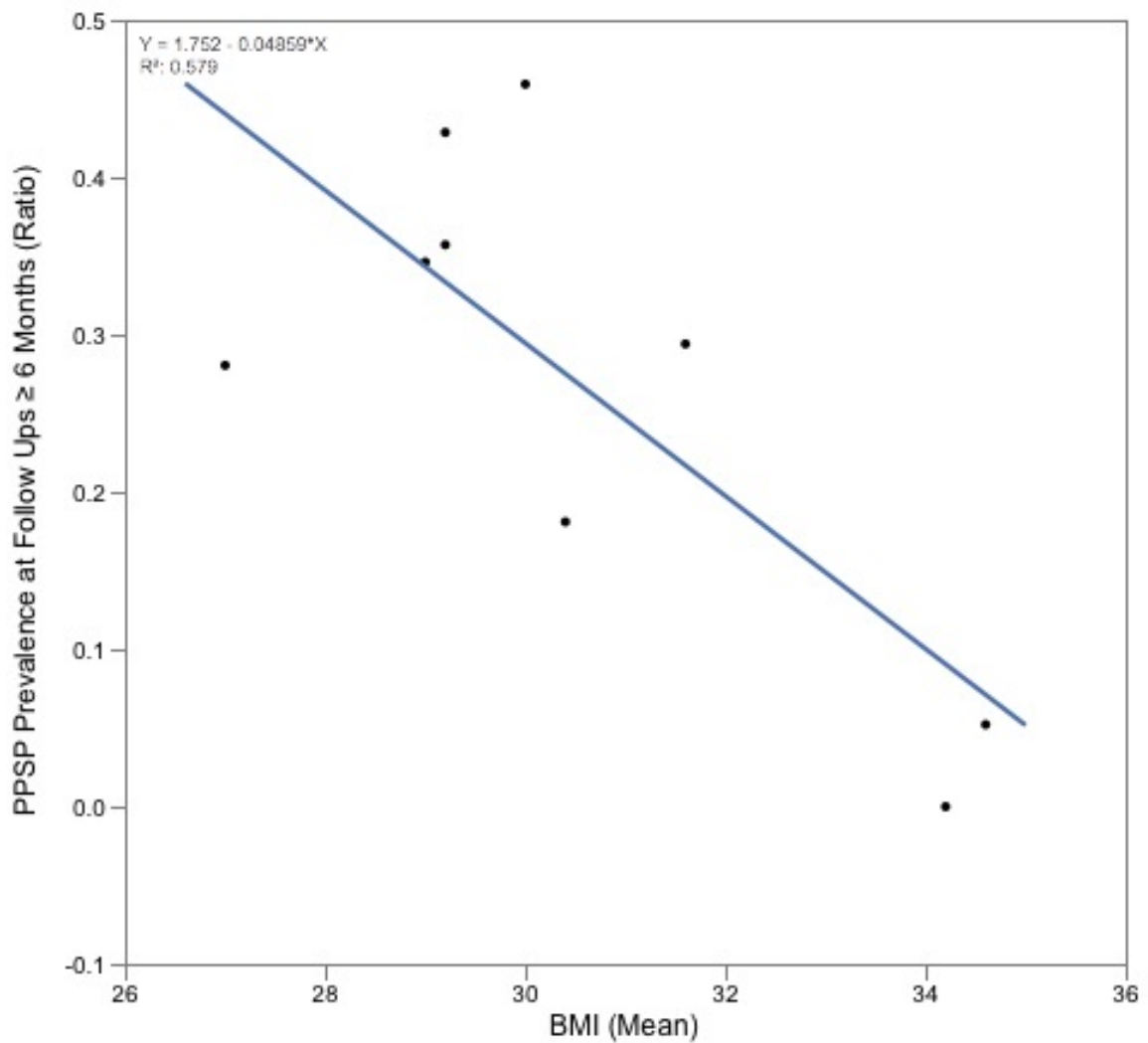


Figure 6. Scatter plot of the PPSP prevalence at follow ups ≥ 6 months (ratio) vs BMI (mean) for THA/TKA. Negative relationship for PPSP rate at follow up greater than or equal to 6 month and BMI presented with a linear equation.

Regression for THA/TKA Surgery

With only a single risk factor presenting a statically significant bivariate correlation, we conducted a regression between BMI mean and the prevalence of

PPSP at follow ups ≥ 6 months. BMI was a statistically significant predictor for the prevalence of PPSP ($F[1,7]=9.608$, $p=0.017$, $R^2=0.579$). The regression indicated that a lower BMI is predictive of higher PPSP prevalence.

Gynecologic Surgery

Of the 19 articles that were identified for PPSP after gynecologic surgery, 3 articles were excluded (2 articles excluded on exclusion criterion 5 and 1 article on exclusion criterion 2). There was a total of 30 arms for the 16 included articles. APPENDIX C displays the reporting frequency of all variable for the Gynecologic surgery group.

Bivariate Analysis of Gynecologic Surgery

There was significant positive correlation between mean age and the prevalence of PPSP at first follow up (PPMCC=0.492, $p=0.02$, $n=22$) presented in Figure 7. Additionally, there was another positive correlation between the reported percentage of patients with previous surgeries and the prevalence of PPSP at follow ups ≥ 6 months (PPMCC=0.842, $p=0.009$, $n=8$) presented in Figure 8.

Between the risk factors for PPSP, three correlations were found. A positive correlation was found between age reported at mean/median and the reported percentage of patients with presurgical chronic pain (PPMCC=0.839, $p=0.018$, $n=7$; PPMCC=0.992, $p=0.008$, $n=4$). Furthermore, a positive correlation was seen between the reported percentage of patients with presurgical chronic

pain and the reported percentage of patients with previous surgeries

(PPMCC=0.962, p=0.002, n=6).

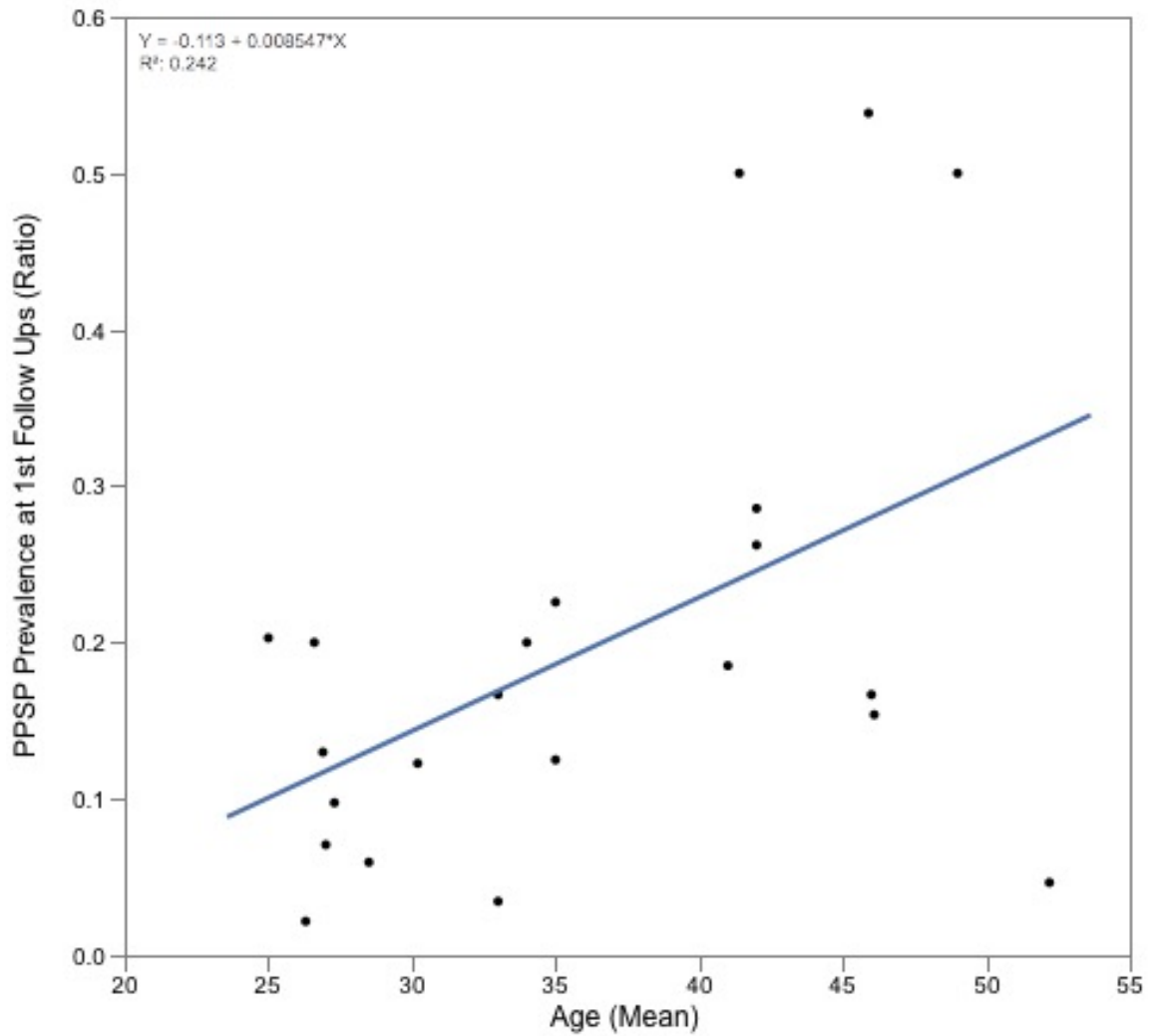


Figure 7. Scatter plot of the prevalence of PPSP at first follow up (ratio) vs. age (mean) gynecologic surgery. Positive relationship between PPSP prevalence at first follow up and age presented with linear equation.

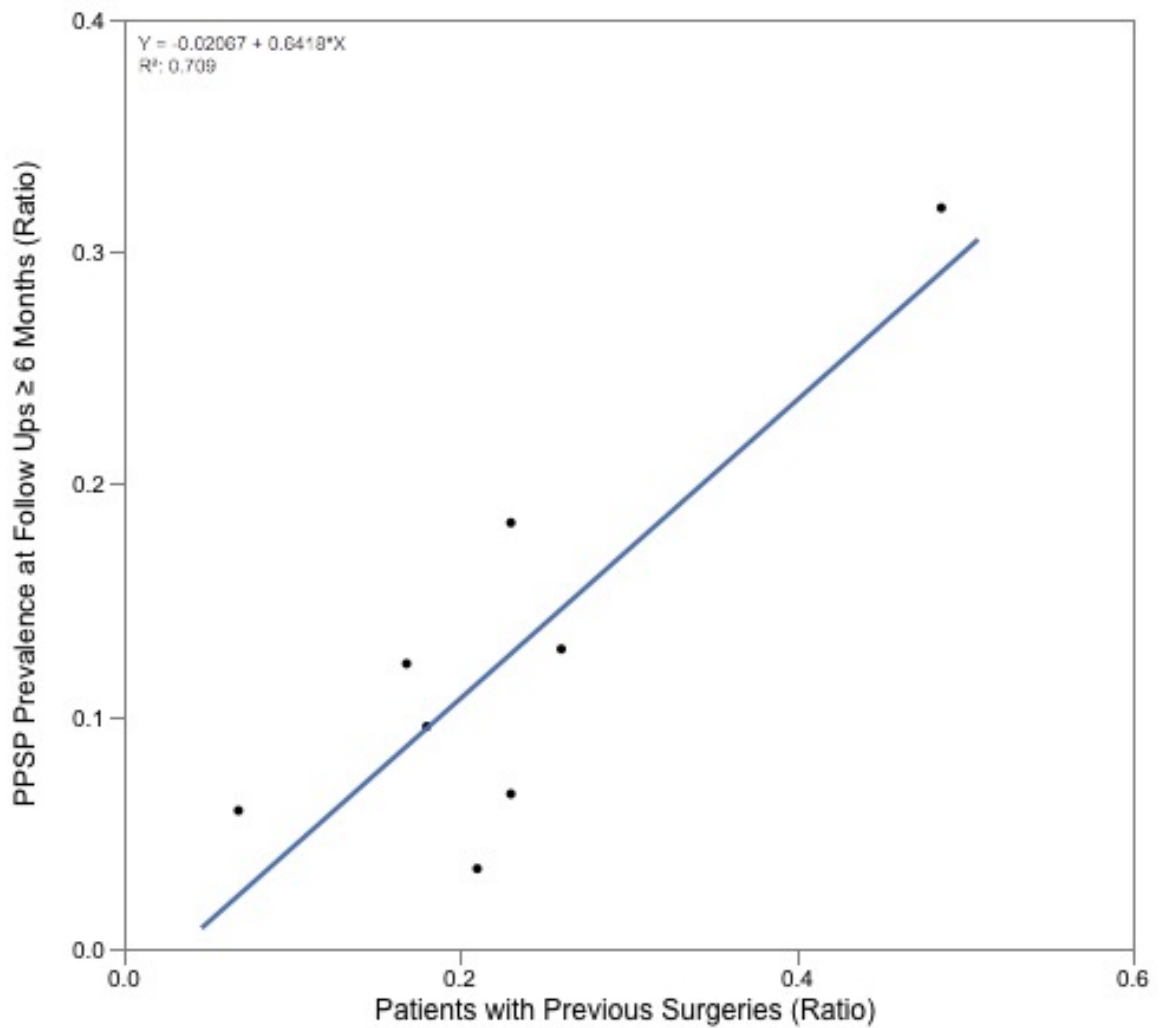


Figure 8. Scatter plot of the PPSP prevalence at follow ups \geq 6 months (ratio) vs patient reported with previous surgeries (ratio) gynecologic surgery. Positive relationship of PPSP prevalence at follow ups greater than or equal to 6 months presented with a linear equation.

Regression of Gynecologic Surgery

Based on the bivariate correlation and the PPSP outcome group, mean age and percentage of patients with previous surgeries were considered in

independent regressions. Mean age was a statistically significant predictor for the prevalence of PPSP at first follow-ups ($F[1,20]=6.393$, $p=0.020$, $R^2=0.242$). The regression indicated higher age is predictive of higher PPSP prevalence. For predicting prevalence of PPSP at follow ups ≥ 6 months, the previous surgery was a significant predictor ($F[1,6]=14.604$, $p=0.009$, $R^2=0.709$). Previous surgery predicted higher prevalence of PPSP at follow-ups greater than or equal to 6 months.

Groin Hernia Repair

Of the 141 identified articles in the search 24 were excluded from the analysis and a total of 180 arms. APPENDIX C displays the reporting frequency of all risk factors analyzed for the groin hernia repair group.

Bivariate Analysis of Groin Hernia Repair

As with the total studies, the large number of arms for the groin hernia repair group created negatively skewed dependent outcomes therefore prevalence of PPSP was normalized by the square root function. Prevalence of PPSP at first follow-ups positively correlated with BMI median (PPMCC=0.615, $p=0.007$, $n=9$) and longer surgery duration (PPMCC=0.243, $p=0.020$, $n=92$) as shown in Figure 9, 10, and 11. Additionally, prevalence of PPSP follow-ups ≥ 6 months positively correlated between the median BMI (PPMCC=0.755, $p=0.019$, $n=9$) and the percentage of patients reported with presurgical chronic pain (PPMCC=0.552, $p=0.027$, $n=16$) as shown in Figure 12.

Between the risk factors for PPSP, there were significant correlations between age median and surgery duration (PPMCC=-0.922, p=0.003, n=7); age mean and BMI mean (PPMCC=0.620, p=0.006, n=18); percentage of smokers and BMI mean (PPMCC=-0.946, p=0.015, n=5); and percentage of patients with previous surgeries correlated with longer surgery duration (PPMCC=0.0614, p=0.026, n=13).

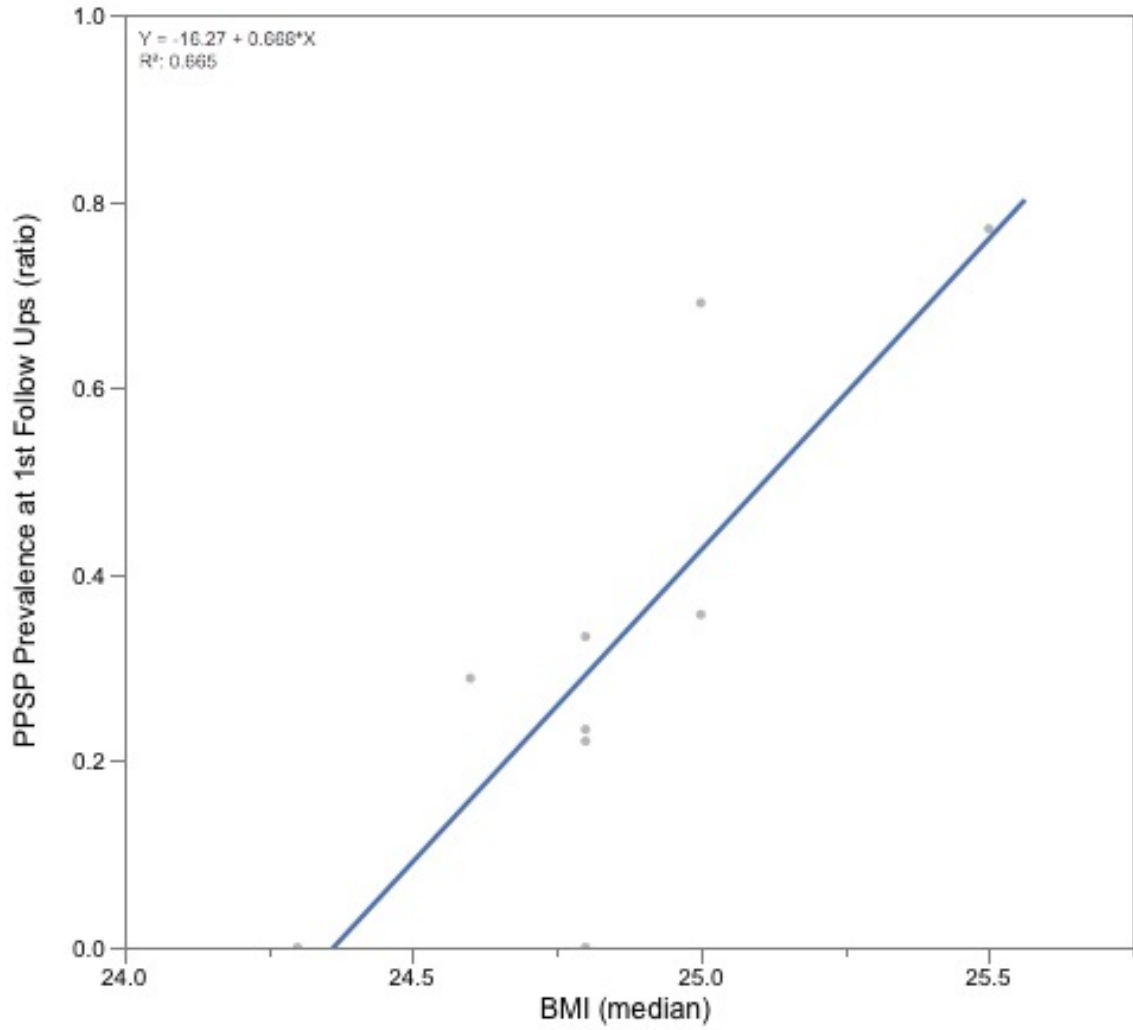


Figure 9. Scatter plot of the PPSP prevalence at first follow up (ratio) vs. BMI (median) for groin hernia repair. Positive relationship between PPSP prevalence and BMI presented with linear equation.

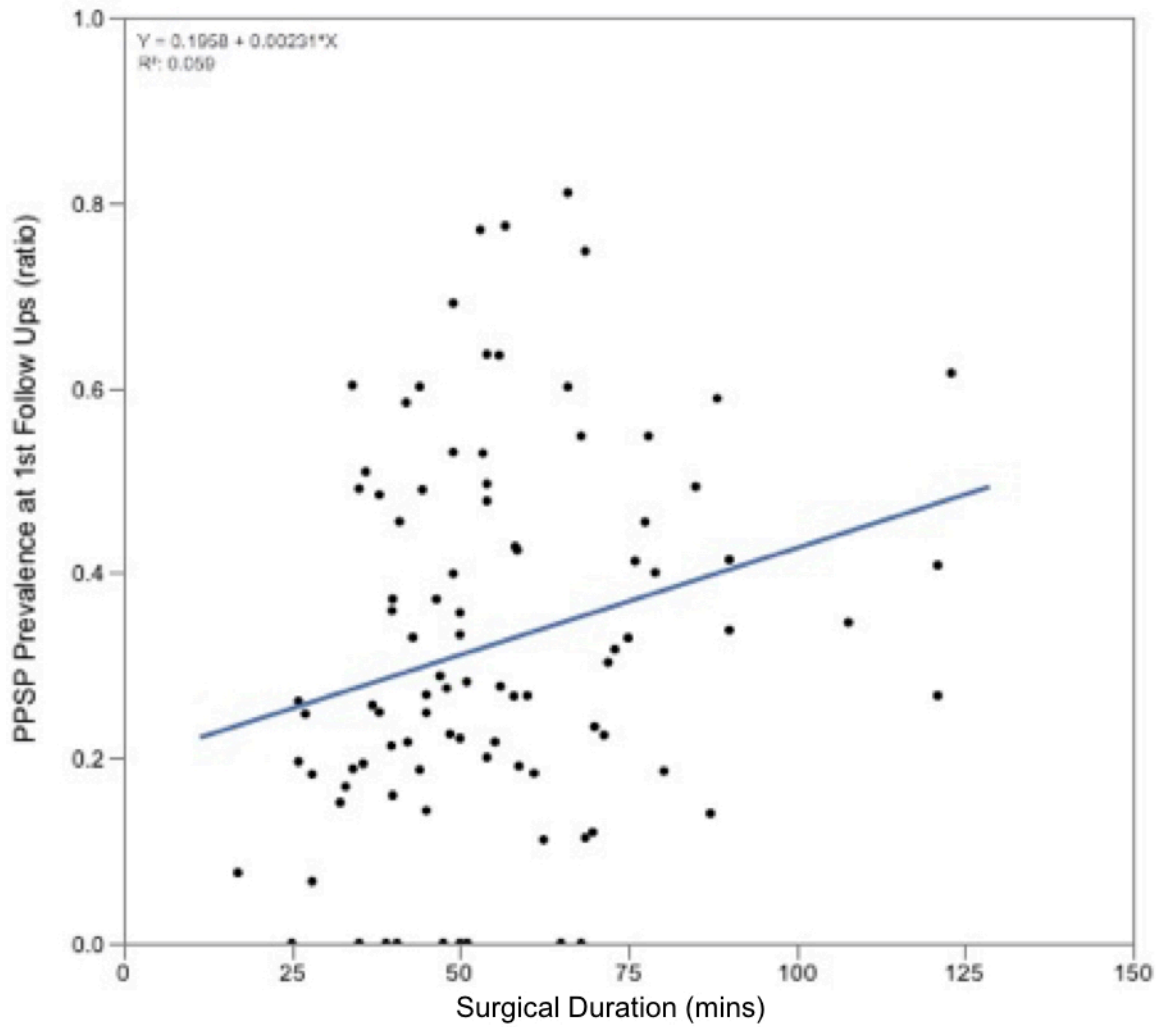


Figure 10. Scatter plot of the PPSP prevalence at first follow up (ratio) vs surgical duration (mins) for groin hernia repair. Positive relationship between PPSP prevalence and longer surgical duration presented with a linear equation.

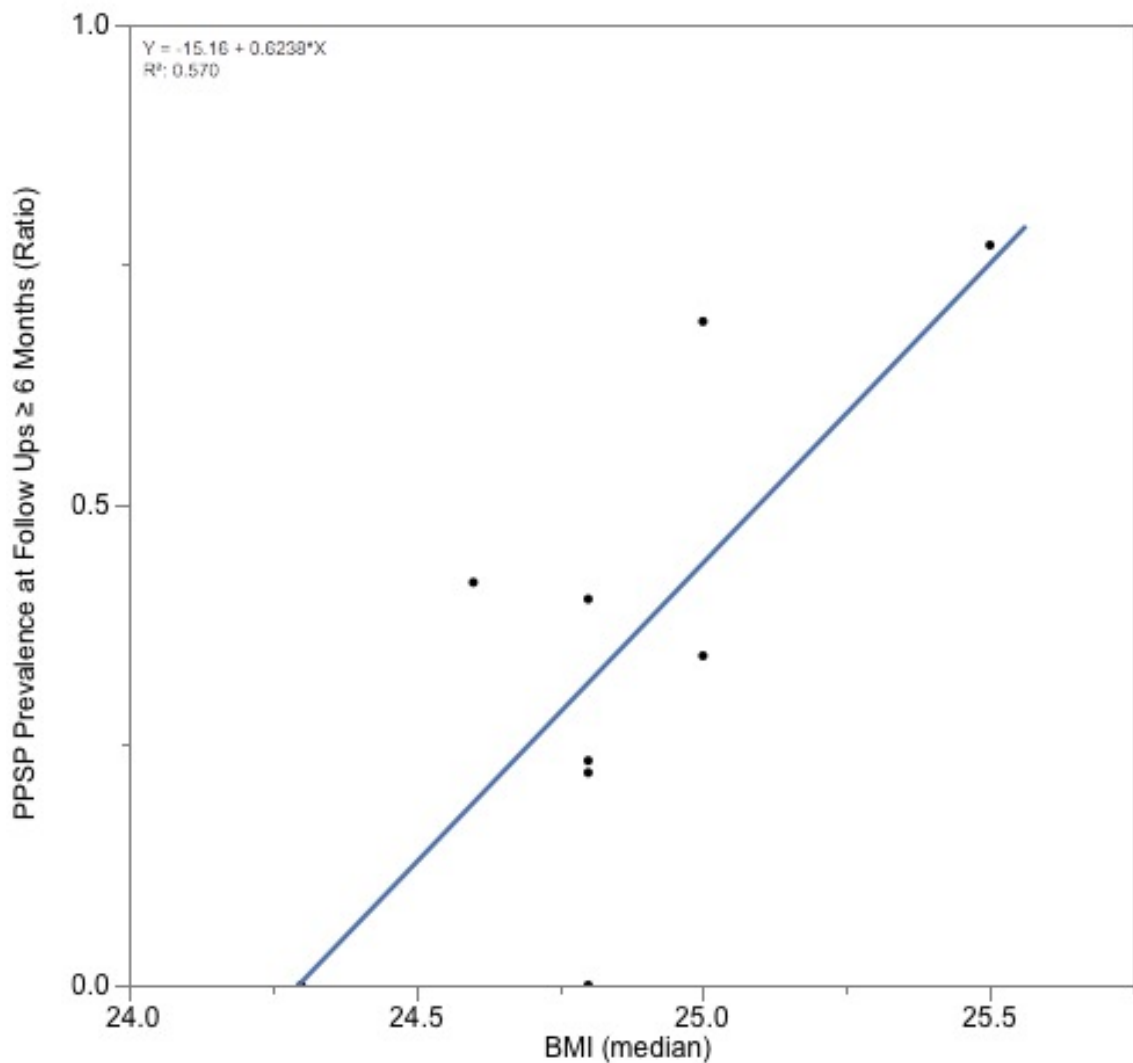


Figure 11. Scatter plot of the PPSP prevalence at follow ups \geq 6 months (ratio) vs. BMI (median) for groin hernia repair. Positive relationship with higher R^2 between PPSP prevalence at follow ups greater than or equal to 6 months and BMI presented with linear equation.

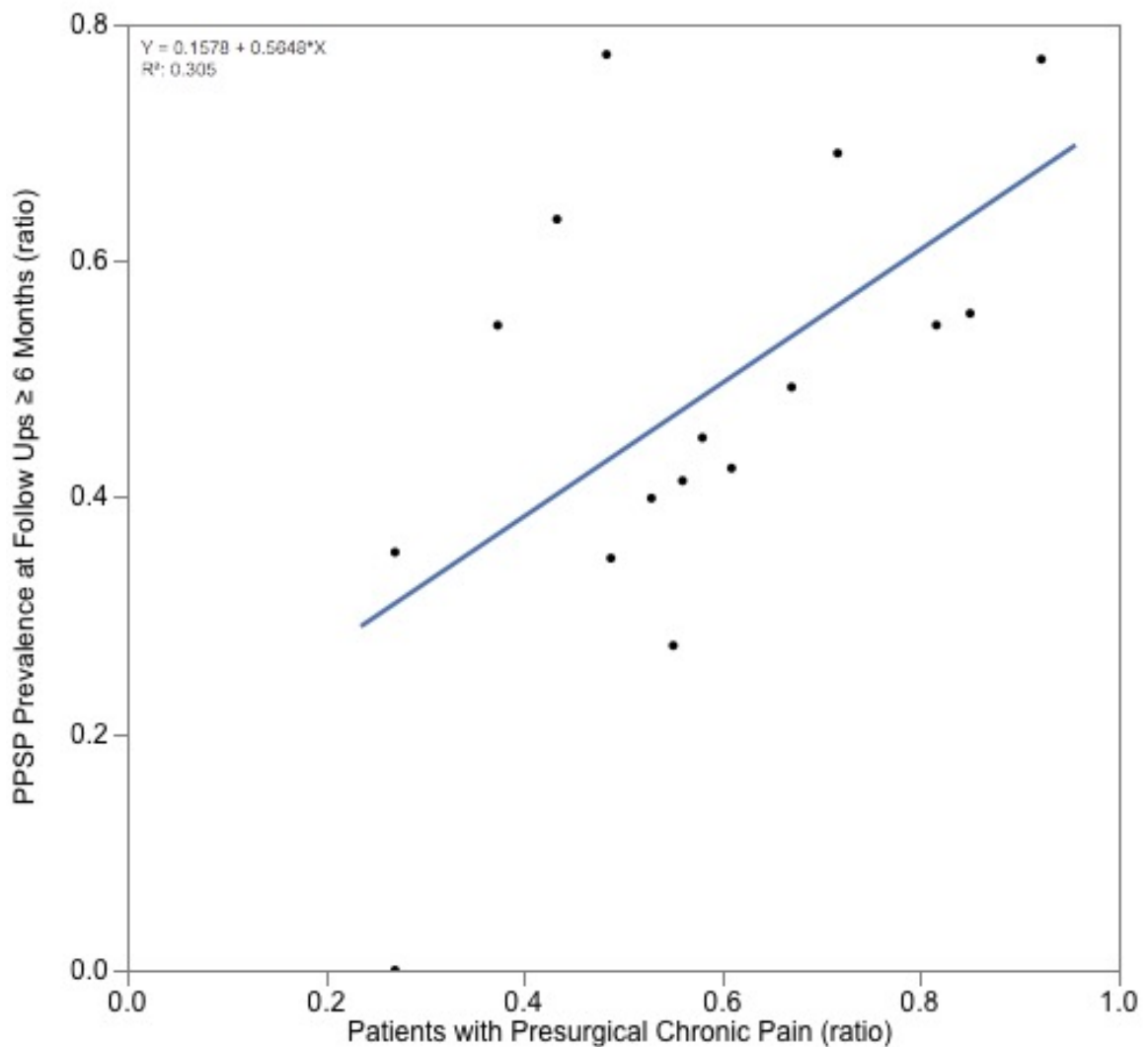


Figure 12. Scatter plot of the PPSP prevalence at follow ups \geq 6 months (ratio) vs. patient reported with presurgical chronic pain (ratio) for groin hernia repair. Positive relationship shown between PPSP prevalence at follow ups greater than or equal to 6 months and presurgical chronic pain presented with linear equation.

Regression of Groin Hernia Repair

The two factor regression model including BMI median and surgical duration for predicting the prevalence of PPSP at first follow-ups is

statically significant ($F[2,6]=5.970$, $p=0.037$, $R^2=0.667$). Longer surgery duration and higher BMI is predictive of higher prevalence of PPSP after groin hernia repair ($\beta = 0.001$ and $\beta =0.661$). One study included both BMI median and percentage of patients with presurgical chronic pain therefore, independent regression models were conducted for each factor. BMI median was significant predicted the prevalence of PPSP at follow-ups greater than 6 months ($F[1,7]=9.266$, $p=0.019$, $R^2=0.570$). Higher BMI was predictive of PPSP prevalence ($\beta =0.624$). Presurgical chronic pain was significant predicted the prevalence of PPSP at follow-ups ≥ 6 months ($F[1,14]=6.141$, $p=0.027$, $R^2=0.305$). Higher rate of presurgical chronic pain was a statically significant predictor of PPSP prevalence ($\beta =0.565$).

Iliac Crest Bone Harvest

Of the 30 articles identified in the search, 11 articles were excluded leaving a total of 19 studies with 29 arms. APPENDIX C displays the reporting frequency of all risk factors analyzed for the iliac crest bone harvest group.

Bivariate Analysis of Iliac Crest Bone Harvest

No risk factor for iliac crest bone harvest was found to be statistically significant. However, there was evidence of tendency between the percentage of smoker reported and the prevalence of PPSP at first follow-up (PPMCC =0.807, $p=0.099$, $n=5$).

Regression of Iliac Crest Bone Harvest

A regression was conducted for further evidence of correlation between smoking and the prevalence of PPSP at iliac crest bone harvest and statistical significance was not found ($F[1,3]=5.596$, $p=0.099$, $R^2=0.651$).

Study 2 - Cross-sectional Survey

Patients over 18 years of age who have undergone cystectomy for bladder cancer between Jan 1, 2009 to Nov 30, 2015 at Washington University/Barnes-Jewish Hospital were considered for participation in the survey, and those meeting inclusion criteria were contacted. 437 patients were identified. 163 patients had deceased and 144 responses returned. Out of the 144 responses, 16 patients refused to participate in the study, and 24 additional returned questionnaires indicated that the patient had deceased. The response rate was 45.5%. At this time, follow-up attempt to contact the patients that did not respond to the survey was not completed. A total of 104 responses were included in the analysis (Figure 13).

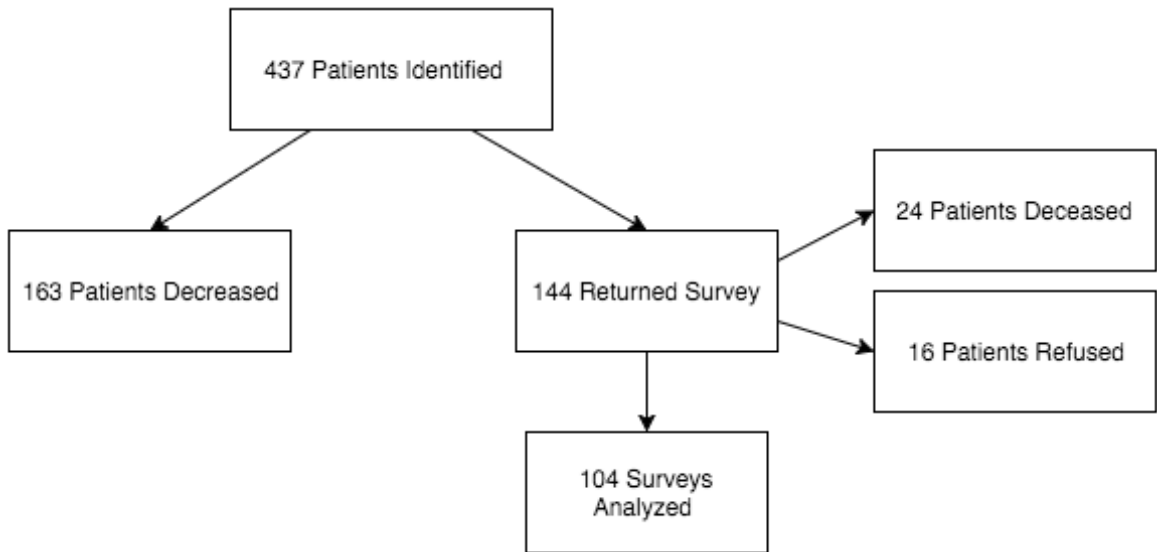


Figure 13. Cystectomy patient response flow chart Out of the patients identified, 144 returned the survey and 104 survey were completed, which were used in the analysis.

Patient Demographics

At the time of the surgery the mean age was 68.40±9.2 (range 44-86). 87 of the patients were male (83.7%). 76 of the patients were identified as Caucasian (73.1%), 6 patients were identified as African American (5.8%), and for 21 patients the race was not identified (20.1%).

PPSP Prevalence

Of the returned the returned questionnaires 23 patients stated that they did have pain in pelvic region in the past week. We determined a PPSP point prevalence rate of 22.1% for patients undergoing cystectomy at the time of survey. Twenty-eight patients stated that they did have pain in the pelvic region within the past 2 months indicating a slightly higher PPSP prevalence rate of 35.9%. There

was a statistically significant difference between males and females reporting PPSP ($p=0.005$, Fisher's exact test).

Presurgical Chronic Pain

Twenty-six patients (25.0%) reported having pain prior to surgery. Ten patients (43.5%) reported pain prior surgery and continued to have pain after the surgery. Sixteen patients (19.8%) reported pain prior to surgery but indicated that the pain had resolved at the time of survey. The prevalence of PPSP significantly differs between male/female sex and patients with presurgical chronic pain ($p=0.05$, $p=0.03$; Fisher's exact test). Female sex is associated with 5.26 greater odds of PPSP occurrence (OR = 5.21, 95% CI 1.68-16.22, $P=0.05$) and presurgical chronic pain is associated with 3.13 greater odds of PPSP occurrence (OR=3.13, 95% 1.16-8.40, $P=0.03$). No difference was found between the severity level reported for presurgical pain as presented in Table 4.

Surgical Features

Radical robotic-assisted laparoscopic cystectomy was scheduled for 28 patients and open cystectomy was scheduled for 76 patients. Twenty-one patients were scheduled for a total cystectomy and 51 patients were scheduled for cystectomy with ileal conduit. For two patients, nephrectomies were performed in addition to cystectomies. For one patient, hip hardware was removed and a cystectomy was performed. one-hundred surgeries were performed under general anesthesia and 4 surgeries had general and epidural anesthesia.

Sensory Changes

Twenty-five patients (24.0%) reported sensory changes; 19 patients (18.3%) had decreased sensations (hypoesthesia) and 6 patients (6.8%) had increased sensations (hyperesthesia_ over the skin around the surgical scar. Hyperesthesia was associated with 8.53 greater odds of PPSP occurrence (OR = 8.53, 95% CI 1.43-51.01, P=0.02).

Table 4. Characteristics of cystectomy survey responders. The frequency, count, and p-value of patients with pain and without pain analyzed for risk factors for prevalence of PPSP after cystectomy.

	Total population	Patients with pain	Patients without pain	Between “pain” and “no pain” groups: P-Value or OR (95% CI)
Number of Responses (response rate)	104 (45.5%)	23	81	
Age, years, mean (SD)	68.4 (9.20)	65.4 (8.31)	69.2 (9.31)	p = 0.08
Sex				
Male	87	14	73	p = 0.005*
Female	16	8	8	5.21 (1.68-16.22)
Self-reported presurgical pain	26 (25%)	10 (43.5%)	16 (19.8%)	p = 0.03* 3.13 (1.16-8.40)
Presurgical pain severity				Mild vs Moderate p = 0.66
Mild	8	2	6	Moderate vs Severe p = 1.0
Moderate	13	5	8	Milder vs Severe p = 1.0
Severe	8	3	5	
Time since surgery, months, mean (SD)	26.1 (18.2)	22.6 (19.37)	27.09 (17.88)	p = 0.30
Race				
White	76	14	62	
Black	6	-	6	
Unknown	21	9	13	
Anesthesia Duration, minutes, mean (SD)	488.7 (176.7)	465.5 (144.5)	494.8 (184.5)	p = 0.50
Hypoesthesia, n (%)	19 (18.3%)	4 (17.4%)	15 (18.5%)	p = 1.00
Hyperesthesia, n (%)	6 (6.8%)	4 (17.4%)	2 (2.5%)	p = 0.02* 8.53 (1.43-51.01)

DISCUSSION

Study 1 – Systematic review and meta-analysis

All Surgical Types

A systematic review and meta-analysis was conducted to investigate and provide an updated evaluation on major risk factors for PPSP to better understand and possibly prevent this condition. Results for all cases showed that age and surgical duration were associated with the development of PPSP. However, regression models did not identify significant universal risk factors that could predict PPSP across all surgical groups. This result could be attributed to the variation of multiple factors among the surgical groups. The systematic review also determined that there is standardized substantial variability in the method for reporting PPSP. Additionally, there is a lack of standardized assessments for psychological factors in regards to PPSP. Depression was measured on 4 differing scales: Hospital Anxiety and Depression Scale (HADS), Epidemiologic Studies-Depression, Becks Depression Index, and Spielberger's State-Trait Anxiety Inventory (STAI) for Depression. There were two different assessment tool for Anxiety (HADS and STAI) and three assessment tool for catastrophizing: Pain catastrophizing scale (PCS), Coping Strategies Questionnaire (CSQ), and Coping Strategies Questionnaire-Revised. The variety of scales for psychological factors did not allow meaningful comparison across

studies, showing that a uniform assessment method for PPSP can be beneficial in allowing between study comparisons.

Breast Surgery

In assessing the risk factors for breast surgery, we found that smoking was a risk factor for PPSP development. It has been reported that patients that are smokers are more likely to develop PPSP (Sipilä *et al.*, 2012; O J Vilholm, Cold, Rasmussen, & Sindrup, 2008) but the finding is inconsistent across studies (O. J. Vilholm, Cold, Rasmussen, & Sindrup, 2009; Von Sperling, Hoimyr, Finnerup, Jensen, & Finnerup, 2011). The significant bivariate correlation and non-significant regression could be attributed to the variation across the extracted studies. For this surgical group, longer surgery duration was less likely to lead to PPSP development.

Thoracic Surgery

Based on the results for thoracic surgery, males and patients with lower BMI were associated with higher rates of PPSP. This finding was contradictory to findings in the literature (Bruce *et al.*, 2003; Grosen, Laue Petersen, Pfeiffer-Jensen, Hoejsgaard, & Pilegaard, 2013; Ochroch *et al.*, 2002; Peng *et al.*, 2014). The meta-analysis included a variety of surgical procedures of the thoracic group which could possibly cause the deviation from literature. Also we found that higher age is associated with longer duration of surgery. Older patients requiring more complex thoracic surgical inventions could possibly explain this outcome (Limmer, Unger, Czymek, Kujath, & Hoffmann, 2011).

THA/TKA

For the THA/TKA surgical group, BMI was the only risk factor found that was associated with PPSP development. Lower BMI was predictive of PPSP. The evidence in literature is contradictory; BMI was associated with more pain at 6-12 months and 2-5 years post operatively for THA (Braeken, Lochhaas-Gerlach, Gollish, Mylés, & Mackenzie, 1997; Singh & Lewallen, 2010), in two studies but other studies found no association (Busato *et al.*, 2008; Jones, Voaklander, Johnston, & Suarez-Almazor, 2001; Pinto, McIntyre, Ferrero, Almeida, & Araújo-Soares, 2013; Roder *et al.*, 2003). As expected, presurgical chronic pain was associated with preoperative opioid usage. Patients with presurgical chronic pain were more likely to use preoperative opioids for pain relief.

Gynecologic Surgery

In assessing the risk factors for gynecologic surgery, we found that higher age and previous surgeries were risk factors for PPSP development. In contrast to other studies (Brandsborg, Dueholm, Nikolajsen, Kehlet, & Jensen, 2009; Loos, Scheltinga, Mulders, & Roumen, 2008) which determined no association between age and PPSP, our finding showed that older patients were more likely to develop PPSP. Mechanisms explaining the increased incidence of chronic pain in older patients are unknown, but epidemiological surveys suggest that the prevalence of pain increase with age, and women are generally more likely to report persistent pain than men (Tsang *et al.*, 2008). Based on the results, it is

clear the presurgical pain is a risk factor. This risk factor is supported by multiple studies that show presurgical pain (both pelvic and remote) associated with an increased risk of PPSP (Brandsborg *et al.*, 2009; Kainu, Sarvela, Tiippana, Halmesmäki, & Korttila, 2010; Pinto, McIntyre, Nogueira-Silva, Almeida, & Araújo-Soares, 2012; VanDenKerkhof *et al.*, 2012). Additionally, both risk factors are supported by the associated between age vs. presurgical pain and presurgical pain vs previous surgeries.

Iliac Crest Bone Harvest

Based on the results, no risk factor was associated with PPSP. However, we found evidence that suggested smoking status correlating with PPSP development which is supported in a single ICBH study (Resnick, 2005). Smoking status relation to PPSP may come from the association of poor bone healing with smoking (Hadley & Reddy, 1997).

Groin Hernia Repair

Higher BMI and surgery duration were found as risk factors for PPSP for groin hernia repair. BMI as a risk factor is supported by a prospective study of 1,440 inguinal hernia repairs which showed that BMI was associated with pain in a multivariate analysis (Massaron *et al.*, 2007). Longer surgical duration as a risk factor is additionally supported by the results of the analysis of all surgical groups and is in accordance with literature (Peters *et al.*, 2007).

Study 2 - Cross-sectional Survey

This study confirms persistent postsurgical pain complication following cystectomy. Persistent pain occurred in 22.1% of patients following cystectomy at a mean follow-up time of 26.1 months. The pain was often mild, but 30% of patients with PPSP had moderate pain and 17.4% had severe pain. With an estimated 74,690 incident cases from bladder cancer in 2014 and an approximated rate of 9.02% receiving cystectomy for patients diagnosed with bladder cancer, this would result in 1,450 patients developing chronic iatrogenic pain yearly following cystectomy in the US alone (Konety, Dhawan, Allareddy, & Joslyn, 2005; Yeung, Dinh, & Lee, 2014). Although, other studies have not reported PPSP after cystectomy, a few studies have reported the overall postoperative complication rates between 18.0-31.9% (Avritscher *et al.*, 2006; Konety & Allareddy, 2007). Our PPSP rate of 22.1% is in accordance with previous overall complication rates.

The response rate was 45.5% but no attempt was made yet in contacting the non-responding patients. This is suggestive that the current sample may not be representative of the whole population. We expect an increase in response rate over next several weeks with further attempts to contact patients that did not complete the survey.

We found that patients with pain tended to be younger than patients without pain, however this difference was not significant. Other studies have

found that younger age predicts chronic pain but with inconsistency (Kalkman *et al.*, 2003; Katz & Seltzer, 2009)

Reported number of males/females (87/16) was expected, since it has been reported bladder cancer occurs primarily in males (Kaufman *et al.*, 2009). In accordance with other studies, we found that females showed increased prevalence of PPSP, but the small sample size needs to be considered (Blyth *et al.*, 2003; Schnabel & Pogatzki-Zahn, 2010).

Overall Discussion?

This study confirmed the association between presurgical pain and the development of PPSP which has been found to be one of the most consistent patient-related risk factors (Katz & Seltzer, 2009; Macrae, 2008; O J Vilholm *et al.*, 2008).

We found a statistically significant association between sensory abnormalities and persistent pain suggesting that PPSP might be of neuropathic origin in some patients. We hope that our planned sensory examination of these patients may elucidate this question. In present study, we found only hyperesthesia to be linked with long term pain similar to a Norwegian study that investigated the prevalence and factors associated with PPSP and sensory changes for augmentation mammoplasty (Kaasa, Romundstad, Roald, Skolleborg, & Stubhaug, 2010).

Our meta-analysis showed that chronic pain is a complex experience that has multiple factors which may not be related across surgical groups, from our study a valid assessment method for PPSP was determined. Preoperative factors such as age, BMI, sex presurgical pain, and previous surgeries were all significant risk factors but on different surgical groups. Intraoperative factors such as surgery duration for all cases showed evidence of association with PPSP development. Additionally, the survey on PPSP following cystectomy provided support for the risk factors identified in the meta-analysis.

Based on our analyses, we suggest that researchers consider collecting the following factors when performing PPSP studies: age, BMI, diabetes mellitus status, presence of presurgical pain, preoperative psychological factors, previous surgery, and preoperative opioid usage. Additionally, patient demographics such as age and BMI should be reported in consistent descriptive statistics (mean and standard deviation) to allow for more meaningful meta-analyses in the future. Although presented in a few studies, psychological risk factors were limited and not evaluated because of the discrepancy in the assessment methods. For standardized PPSP assessment, psychological factors should utilize the following instruments for comparisons within and across surgical groups: Beck's Depression Inventory for depression, State-Trait Anxiety Inventory for anxiety, and Pain Catastrophizing Scale for catastrophizing based on their current frequency of reporting for studies on PPSP.

Limitations of Study 1

Despite the availability of a large amount of studies, many studies have not assessed most of the risk factors that have been previously reported to be associated with PPSP. Therefore, the eventual analysis of each risk factor had to rely on a relatively limited amount of studies that have reliably reported the specific risk factor. For example, risk factors such as psychological factors and pre-existing diabetes, both that were previously identified in the literature, were reported only 2.75% and 4% of the overall studies. In our analyses, these were not significantly associated with PPSP development. The limited number of available studies may be one of the reasons for these inconsistent results, considering that individual studies have carefully demonstrated these associations.

There is also evidence that psychological factors and other preoperative factors were contradictory or inconclusive, possibly due to lack of standardized assessment methods.

The bias assessment showed that 16.7% of the studies contain at least some sort of potential bias. Studies with bias were assessed if possible but the studies could have led to outliers for the prevalence of PPSP reported.

Limitations of Study 2

With a response rate of only 45.5%, the sample of cystectomy patients may not be representative of the population. The moderate response rate could also be a factor for the higher than expected PPSP prevalence of 22.1%. Since

the cross-sectional study is not complete, we do expect the response rate to increase.

With a retrospective collection of baseline data, the existence of presurgical pain data may contain recall bias. To reduce this, the questions on the survey were formulated to prevent recall bias. Consistent with 5-year survival rates after cystectomy, many patients have died, so PPSP data in these subjects cannot be determined (Yeung *et al.*, 2014).

Implications for Future Research

As determined by the meta-analysis the development of PPSP is likely to be multifactorial, involving preoperative, and postoperative psychological and biological factors, as well as intraoperative surgical characteristics. The fact that certain risk factors were not significantly associated with the development of PPSP may indicate additional unidentified predictive risk factors for PPSP. It would be of interest to examine the mechanisms that lead to PPSP based on the risk factors identified. This further analysis could introduce new targets for the prevention and treatment persistent post-surgical pain.

Based on the resulting risk factors from the meta-analysis, standardized assessment of PPSP should include age, BMI, presurgical pain, preoperative psychological factors, previous surgery, and preoperative opioid usage. Utilizing a comprehensive and standardized PPSP assessment, as determined by this meta-analysis, would allow for imperative comparisons within and across surgical groups for future studies to identify the complex patterns for PPSP development.

Lastly, the substantial prevalence of persistent pain after cystectomy has been identified which was unknown prior to this study. For future studies, it would be of importance to stratify patients by risk, and test interventions to reduce the prevalence of PPSP.

APPENDIX A



Washington University in St. Louis

SCHOOL OF MEDICINE

Department of Anesthesiology
Division of Clinical and Translational Research

This survey is about your specific health and pain as it relates to your bladder surgery. Please provide one answer for each question. Check the box next to your answer, where appropriate. If you are unsure how to answer a question, please choose the one that fits best to the best of your memory. You may skip questions you wish not to answer.

The questions asking about pain in the **pelvic region** refer to pain anywhere between your belly button and groin, including the area of the scar from your bladder surgery.

The **first and second** questions concern the time **before** the bladder surgery.

1. Did you have pain in the pelvic region before your bladder surgery?

Yes

No →

If No, skip question 2, move to

question 3

2. What was your average pain level before surgery?

Put a mark on the line below to indicate pain level:



The following questions concern the time **after** the bladder surgery.

3. For how long after the surgery did you have pain in the pelvic region?

Yes

No →

If No, skip question 8 & 9, move to

question 10

8. Among the following words, circle those words that describe your pelvic pain

aching

throbbing

shooting

stabbing

gnawing

pricking

sharp

tender

burning

exhausting

tiring

penetrating

nagging

numb

miserable

unbearable

dull

radiating

squeezing

cramping

deep

Other, please

specify _____

9. How often have you had pain in the pelvic region within the past 2 months?

Constantly

Every day, but not constantly

2 or more days a week

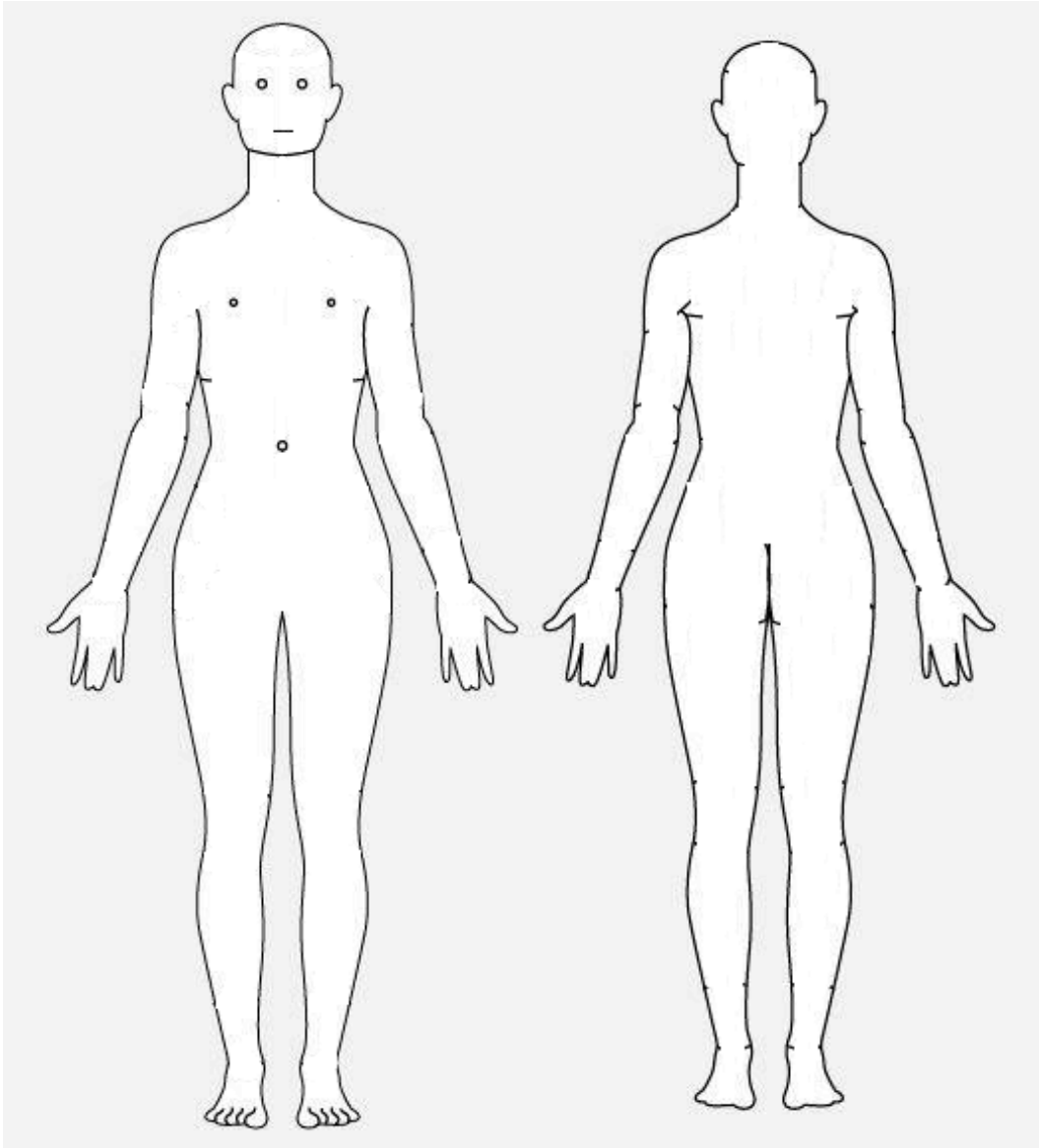
Less than 2 days a week

10. Do you currently have pain that has been present for more than 2 months outside the pelvic region?

Yes

No

11. On the body map below - please shade all area(s) in which you have pain that has been present for more than 2 months:



12. Circle the one number that describes how, during the past 2 months, pain in the pelvic region has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely Interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely Interferes

G. Enjoyment of Life

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere Completely Interferes

13. Do you take any medication for the pain in the pelvic region?

- Yes → Please specify

- No → **If No**, skip question 14, move to question 15

14. If yes, how often do you take medication for this pain?

- Every day
- 2 or more days a week
- Less than 2 days a week

15. Have you sought other treatments for the pain? (For example, physical therapy or acupuncture)

- Yes → Please specify

- No

16. Did you have additional surgeries in the pelvic region after the bladder surgery?

- Yes
- No

17. Do you currently receive treatment for cancer?

- Yes
- No → **If No**, skip question 18, move to question 19

18. Please select the current cancer treatment (all that apply)

- Chemotherapy
 - Radiation
 - Other, please specify
-

19. We would appreciate the opportunity to contact you about participating in a brief testing session.

May we contact you by phone or e-mail?

- Yes
- No → **If No, skip question 20**

20. Please fill out with contact information, and mark the box for preferred method of communication.

Phone _____

Best time for phone

calls _____

Email
Address _____

Thank you for your participation!

APPENDIX B

Extracted by _____ Date: (MM/DD/YY)_ 5/5/15

General study data

First Author (e.g. Smith, AB)	
Year Published (YYYY)	
Title	
Journal	
Role of funding source	1) funded by pharma or device industry, 2) funded by public (e.g. NIH) or foundation grants, 3) both industry and non-industry, 4) not funded, 5) unclear or other

Criteria for including study

1. Surgery belongs to one of the following categories: <i>i) thoracic surgery, (ii) breast surgery, (iii) major abdominal surgery on the GI tract, (iv) donor nephrectomy, (v) gynecologic surgery (hysterectomy and C section), (vi) prostatectomy, (vii) groin hernia repair, (viii) total hip arthroplasty (THA) or knee arthroplasty (TKA), (ix) iliac crest bone harvest.</i>	No-N Yes-Y	
2. PPSP defined as primary/secondary outcome or specifically described in methods as one of the study objectives?	No-N Yes-Y	
3. PPSP occurrence (incidence/prevalence) reported?	No-N Yes-Y	
4. Includes more than 9 patients per arm?	No-N Yes-Y	
5. At least 2 months follow-up?*	No-N Yes-Y	
6. All patients older than 13 years old?	No-N Yes-Y	

Final decision: if all replies are "**yes**" - include. If "no" - exclude and STOP here

* studies with less than 10% patients having follow-up between 1-2 months will be allowed.

Characteristics of included study

Potential sources of bias assessment:

A. The sample adequately represents the population of interest	Yes/No/Unclear	Overall grading
1. Is the population of interest adequately described for key characteristics (age, gender, reason for surgery)?		Yes (if all 3 are met) Partly (if 1-2 of 3 are met, ≤1 Unclear) No (if none is met)
2. Sampling frame and recruitment adequate (sample data include all patients undergoing the surgery in the reported period)?		
3. Inclusion and exclusion criteria for the study adequately described?		Unclear/Unknown (>1 of 3 Unclear)
B. The data represent the sample	Yes/No/Unclear	Overall grading
1. Dropouts: % patients completing the study and reasons to loss to follow-up are provided (flowchart or similar).		Yes (if all 3 are met)
2. Follow-up rate adequate (>75% responders providing outcome data for first follow-up).		Partly (if 1-2 of 3 are met, ≤1 Unclear) No (if none is met)
3. There are no important differences between key characteristics /outcomes in participants who completed vs drop-outs.		Unclear/Unknown (>1 of 3 Unclear)
C. The outcome of interest (chronic pain) is adequately measured to limit potential bias.	Yes/No/Unclear	Overall grading
1. Clear definition of chronic pain is provided.		Yes (if all 3 are met)
2. The outcome measure and method used are adequate to limit misclassification bias.		Partly (if 1-2 of 3 are met, ≤1 Unclear) No (if none is met)
3. PPSP outcomes data reported completely (compared to what is set in the methodology).		Unclear/Unknown (>1 of 3 Unclear)
Other potential serious sources of bias (e.g. selective outcome reporting, use of non-validated		

scales, lack or inappropriateness of sample size calculation, exclusion of important patient sub-groups)		
--	--	--

Surgery details

Type of surgery / Surgical procedure	One of the 9 procedures:
Reason/indication for surgery	
Surgical approach (open, laparoscopic etc)	

Methodology

Study design	<ol style="list-style-type: none"> 1. Prospective study – all data collected prospectively. 2. Mail/phone survey - baseline data collected in a prospective study. 3. Mail/phone survey – baseline data collected from database/medical records 4. Retrospective – both PPSP and baseline data collected from database/medical records. 5. N/A 6. Other (comment) 		
Is there a control group of patients not undergoing surgery?	Yes/no		
Number of groups/arms in the study (It can be 1, or more (per perioperative intervention, surgical approach, or other way that the study was designed). Please rate the number of arms/groups and what they represent			
Single-center (S); Multicenter (M)			
PPSP follow-up (Number and months) (note all relevant follow-ups).	F-U # __ months	F-U # __ months	F-U # __ months
Definition of PPSP (describe how PPSP was defined in the study)			
Pain intensity cut-off (and scale) for PPSP, if reported (e.g. at least moderate; or >2 on 0-10 NRS)			
Relevant exclusion criteria (e.g. pre-existing pain, anxiety, opioid use)			
Number of patients undergoing the surgery (entire study).			
Number of participants per group, if several arms	Arm1	Arm2	Arm3

Number of patients at <u>first</u> follow-up (>2 months) (N)			
Number of patients with PPSP at <u>first</u> follow-up (n). (Conservative estimate, if several reported)			
Number of patients at <u>second</u> follow-up (N)			
Number of patients with PPSP at <u>second</u> follow-up (n). (Conservative estimate, if several reported)			
Number of patients at <u>third</u> follow-up (N)			
Number of patients with PPSP at <u>third</u> follow-up (n). (Conservative estimate, if several reported)			

Postoperative analgesic regimen (check all that apply)

IV PCA (with opioid)	yes/no	
Systemic opioids PRN (non-PCA)	yes/no	
Epidural analgesia (with local anesthetic ± opioid)	yes/no	
Regional (peripheral) anesthesia	yes/no	
NSAIDs and or paracetamol (acetaminophen)	yes/no	
Adjuvant analgesics (gabapentin, ketamine etc)	yes/no	
Not reported / other		

Risk factors - preoperative

	Arm 1	Arm 2	Arm 3
Age for each arm: mean ± SD (CI) (median + range, if so reported)			
Sex: M/F ratio			
BMI (mean/median spread)			
Patients with Diabetes Mellitus (ratio or %, whatever available)			
Patients with previous chronic pain (ratio or %, whatever available)			
Patients with previous use of opioids (ratio or %, whatever available)			
Patients with previous surgeries (ratio or %, whatever available)			
Number of previous surgeries per patient (average and SD), if available.			

Smokers (ratio or %)			
Presence of depression, dichotomous; (ratio or %)			
Depression score (average and spread) + assessment method			
Presence of anxiety, dichotomous; (ratio or %)			
Anxiety score (average and spread) + assessment method			
Presence of catastrophization, dichotomous; (ratio or %)			
Catastrophization score (average and spread) + assessment method			

Risk Factors, intraoperative

Anesthesia method (General, regional spinal, regional peripheral or combined general/regional)	Arm1	Arm2
Duration of surgery min (average, spread)		

Early postoperative risk factors

Average pain intensity in first 24h (or POD1)	Scale:	Arm 1	Arm 2 etc..
Maximum pain intensity in first 24h (or POD1)	Scale:		
Other pain intensity parameters collected (pain at rest, moving, coughing etc..)	Scale:		
Average intensity of subtypes of pain (e.g. burning pain)	Scale:		
Amount of postoperative analgesics (iv morphine equivalent per first 24h or similar)			

Risk factors that the study has assessed

Risk Factor	Assessment method	Association with PPSP

APPENDIX C

Breast Surgery Descriptive Statistics

	Mean	Std. Deviation	N
PPSP @ 1st F-U	.3465488	.20086126	65
PPSP < 6 months	.4740739	.23561128	20
PPSP > 6 months	.3011131	.15807764	51
Age (mean)	51.16	9.243	48
Age (median)	54.26	10.439	8
BMI (mean)	25.63	2.282	17
BMI (median)	.	.	0
Surgery Duration (mins)	109.43	57.416	23
Depression	3.15	1.350	10
Anxiety	6.2830	12.54116	10
Chronic Pain (%)	.14	.348	65
Opioids (%)	.00	.000	65
Previous Surgeries (%)	.53700000	.533158513	2
Smoking (%)	.20387286	.100511444	7

Thoracic Surgery Descriptive Statistics

	Mean	Std. Deviation	N
PPSP @ 1st F-U	.3675154	.21715750	70
PPSP < 6 months	.4059371	.23810471	30
PPSP > 6 months	.3572283	.21718774	55
Age (mean)	58.93	9.662	53
Age (median)	60.50	8.168	10
BMI (mean)	25.65	2.382	27
BMI (median)	24.50	.577	4
Surgery Duration (mins)	172.09	58.527	32
Depression	1.09	.	1
Anxiety	25.5563	36.14200	2
Chronic Pain (%)	.41933500	.208860471	4
Opioids (%)	.05000000	.	1
Previous Surgeries (%)	.	.	0
Smoking (%)	.30227250	.097931935	4

Gynecologic Surgery Descriptive Statistics

	Mean	Std. Deviation	N
PPSP @ 1st F-U	.2115494	.13648878	30
PPSP < 6 months	.1662045	.11253971	17
PPSP > 6 months	.2112127	.15925597	18
Age (mean)	36.06	8.492	22
Age (median)	39.75	8.500	4
BMI (mean)	27.28	2.053	8
BMI (median)	.	.	0
Surgery Duration (mins)	67.77	22.414	11
Depression	1.00	.	1
Anxiety	3.3333	.	1
Chronic Pain (%)	.34201364	.193871096	11
Opioids (%)	.03466667	.002886751	3
Previous Surgeries (%)	.33420000	.250365866	10
Smoking (%)	.15000000	.056568542	2

Hernia Surgery Descriptive Statistics

	Mean	Std. Deviation	N
PPSP @ 1st F-U	.1427973	.13814860	180
PPSP < 6 months	.1788356	.16965906	33
PPSP > 6 months	.1313118	.12485721	169
Age (mean)	55.51	8.493	130
Age (median)	59.03	4.191	32
BMI (mean)	25.63	2.067	55
BMI (median)	24.84	.324	9
Surgery Duration (mins)	55.38	21.237	92
Depression	1.00	.	1
Anxiety	1.4286	.	1
Chronic Pain (%)	.49144810	.248720460	21
Opioids (%)	.01500000	.	1
Previous Surgeries (%)	.18460214	.135680274	28
Smoking (%)	.29610143	.186365375	14

ICBH Surgery Descriptive Statistics

	Mean	Std. Deviation	N
PPSP @ 1st F-U	.1997279	.15000400	29
PPSP < 6 months	.2164724	.18194336	15
PPSP > 6 months	.1962744	.11754991	16
Age (mean)	46.26	5.350	27
Age (median)	44.00	.	1
BMI (mean)	25.55	1.202	2
BMI (median)	.	.	0
Surgery Duration (mins)	144.50	40.305	2
Depression	.	.	0
Anxiety	.	.	0
Chronic Pain (%)	.55435000	.	1
Opioids (%)	.	.	0
Previous Surgeries (%)	.11011000	.109835041	3
Smoking (%)	.55562400	.392410654	5

THA/TKA Surgery Descriptive Statistics

	Mean	Std. Deviation	N
PPSP @ 1st F-U	.2730978	.15762875	25
PPSP < 6 months	.2527933	.19984334	11
PPSP > 6 months	.2507892	.13879203	20
Age (mean)	64.02	6.784	22
Age (median)	71.00	2.646	3
BMI (mean)	30.83	2.412	13
BMI (median)	27.00	1.414	2
Surgery Duration (mins)	104.05	32.281	6
Depression	.	.	0
Anxiety	2.3038	.90333	2
Chronic Pain (%)	.32459000	.191349987	5
Opioids (%)	.23637667	.156021230	6
Previous Surgeries (%)	.26757500	.140594041	2
Smoking (%)	.27171500	.249700618	2

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