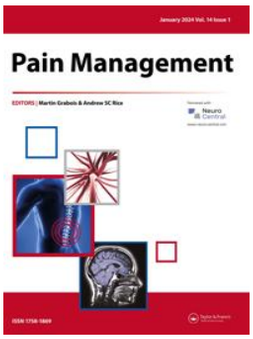

Pain Management

ISSN: 1758-1869 (Print) 1758-1877 (Online) Journal homepage: www.tandfonline.com/journals/ipmt20

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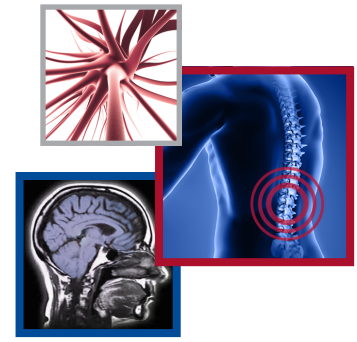
To cite this article: Dagmar CM van Rijckevorsel, Marjan de Vries, Luuk TW Schreuder, Oliver HG Wilder-Smith & Harry van Goor (2015) Risk Factors for Chronic Postsurgical Abdominal and Pelvic Pain, Pain Management, 5:2, 107-116, DOI: 10.2217/pmt.14.47

To link to this article: https://doi.org/10.2217/pmt.14.47

Published online: 25 Mar 2015.

REVIEW

Pain Management



Risk factors for chronic postsurgical abdominal and pelvic pain

Dagmar CM van Rijckevorsel*[1], Marjan de Vries[1], Luuk TW Schreuder[1], Oliver HG Wilder-Smith[2] & Harry van Goor[1]

Practice points

- Chronic postsurgical pain is a common negative consequence of abdominal and pelvic surgery, probably caused by a combination of nerve and tissue damage and alterations in central pain processing.
- Risk factor categories include somatic and psychological patient characteristics, surgical procedure and pre- and acute postoperative pain levels.
- Protective effects have been found for several anesthetic regimens, including epidural analgesia and NMDA-agonist ketamine.
- The strongest predictor of chronic postsurgical abdominal and pelvic pain appears to be preoperative pain.
- Chronic pain as a complication should be taken into consideration and mentioned by clinicians contemplating surgical treatment for their patients.
- Preoperative identification of susceptible patients, addressing risk factors and taking possible protective measures may be helpful in the prevention of chronic postsurgical pain.

SUMMARY Chronic postsurgical pain (CPSP) may develop after any surgical procedure, and is a common feature after abdominal and pelvic surgery with a prevalence varying between 10 and 40%. The pathological mechanisms leading to chronic CPSP are probably inflammation, tissue and nerve damage and alterations in central pain processing. The mechanisms in chronic postsurgical abdominal and pelvic pain are poorly studied and research has largely focused on reporting of prevalence and describing risk factors, including patient characteristics, psychological factors, surgical procedure and pre- and acute postoperative pain. In this review, the most important risk factors are discussed, and aiming for preventive, personalized health care, possible methods for prediction of susceptibility and potential strategies for diminishing chronic postsurgical abdominal and pelvic pain are provided.

KEYWORDS: • abdominal and pelvic surgery • chronic postsurgical pain • prediction • risk factors

Chronic postsurgical pain (CPSP) is increasingly recognized as a potential adverse outcome of surgery and is frequently reported after limb amputation (30–81%), breast surgery (11–57%), thoracotomy (about 50%) and inguinal hernia repair (0–37%) [1–3]. It is often refractory to treatment and thought to be the result of a combination of factors, including inflammation, tissue and nerve damage, and alterations in central pain processing, such as central sensitization and decreased inhibitory pain modulation [4,5].

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The most used definition of CPSP is pain developing after surgery, with other causes for pain excluded and persisting for at least 2 months [6] to 3 months [7]. However, many debate this timeframe, as wound healing and postsurgical inflammation can still persist and pain complaints may decline up to over a year [8–10].

A general population-based survey in Norway showed persistent moderate or severe pain in the anatomical area of surgery in 18.3% of patients who underwent surgery in the preceding 3 years (n = 2043) [11]. In patients visiting chronic pain clinics, surgery is considered the cause of pain in 22.5% [12], and the most frequently affected areas of pain in this group are the abdominal (48%) and anal, perineal and genital regions (38%) [12]. Of the 9 million women in the United States suffering from chronic pelvic pain [13], at least 25% report this as the result of surgery [14].

Two prospective cohort studies of patients who had undergone major abdominal surgery reported a CPSP incidence of 19% after 6 months [3] and an 18% prevalence after 4-year follow-up [10], respectively. Apart from pain, both studies showed poorer functioning and quality of life (QoL) [3,10], and pain-related interference with mood, sleep and enjoyment of life [3].

For the most common pelvic procedure, i.e., hysterectomy, estimated chronic pain percentages vary between 5 and 32% one year after operation [15]. A combined abdominal prostatectomy (n = 45) and hysterectomy (n = 57) cohort showed a CPSP prevalence of about 30% three months after surgery [16]. These percentages are somewhat higher than estimates reported in a systematic review: 11% for various abdominal surgeries, 14% for prostatectomy and 13.7% for gynecologic surgery [17].

Considering the large prevalence of abdominal and pelvic surgeries (67 per 10,000 inhabitants in the Netherlands) [18], the high percentages of chronic postsurgical abdominal and pelvic pain (CPSAPP) and the difficulties in treatment, identifying patients at risk for developing CPSAPP is an important step in the prevention of chronic pain. However, risk factor assessment in CPSAPP has received little attention, in a nonstructured manner and chronic pain mechanistic data are relatively sparse.

In this paper, we review the most common categories of risk and pain-associated factors based on current literature, including patient characteristics, psychological factors, surgical procedures and perioperative pain, and provide tools for identifying patients who are susceptible for developing CPSAPP. In addition, chronic pain mechanism research in abdominal and pelvic and other surgery is summarized. Where there are limited data on important risk factors in abdominal and pelvic surgery, results of other common surgical procedures are presented.

Methods

• Search strategy

Relevant articles were identified in PubMed and the Cochrane library (up to June 2014) using the key words or MeSH terms: postoperative pain, abdomen, pelvis, surgical procedures and susceptibility or risk factors. A total of 64 articles were identified, of which most were not related to risk or associated factors for chronic postoperative pain or focusing on other than abdominal or pelvic surgery. We only included papers on intra-abdominal (visceral) surgery and excluded for example surgery for pelvic floor pathology to increase homogeneity of patients and procedures in this review.

All relevant articles were scanned for relevant references or related articles. Eventually, 11 cohort studies were selected directly or through references or related article search, which are listed in **Table 1**.

Results

In the following section, the alleged risk or associated factors will be addressed and grouped in categories, and are commented on in the comments section.

• Patient characteristics

Several patient characteristics are associated with the development of CPSAPP. Strong risk factors mentioned by several authors are younger age [10,20,26] and female gender. [10,27] Others, however, reported similar age [9,16,19,24,26] and gender distribution in the CPSAPP and non-CPSAPP groups [16,22].

No increased risk was found related to BMI or American Society of Anesthesiologists classification [10,19]. The number of co-morbid conditions and the co-morbid-related disability was associated with more CPSAPP after nephrectomy [22]. Abdominal surgery in patients with a gastrointestinal or other malignancy was associated with less chronic pain than abdominal surgery for benign disease (OR: 0.32; 95% CI: 0.15–0.71) [10].

Table 1. Overview of cohort studies assessing risk factors for chronic postsurgical abdominal and pelvic pain.

Author (year)	Type of surgery	Number (n)	Chronic postsurgical pain incidence/ prevalence	Timing of assessment	Risk factors	Level of evidence	Ref.
VanDenKerkhof *et al.* (2012)	Major abdominal surgery for benign and malignant causes	76	Incidence 19%	Preoperative, 6 weeks and 6 months postoperative	Female gender, preoperative pain, depressive symptoms, anxiety, high expectation of postoperative pain	2b	[3]
Bruce *et al.* (2006)	Major abdominal surgery for benign and malignant causes	202	Prevalence 18%	Preoperative, 4 years postoperative	Female gender, younger age, surgery for benign disease	2b	[10]
VanDenKerkhof *et al.* (2012)	Major elective gynecologic surgery	433	Incidence 14%	Preoperative, 6 months postoperative	Preoperative pain, state anxiety, pain quality descriptors, preoperative opioid consumption, early postoperative pain intensity	2b	[19]
Pinto *et al.* (2012)	Hysterectomy for benign causes	186	Prevalence 50%	Preoperative, 48 h and 4 months postoperative	Age, preoperative remote pain, type of hysterectomy, anxiety, pain catastrophizing, emotional illness representation, early postoperative pain frequency	2b	[20]
Brandsborg *et al.* (2009)	Hysterectomy for benign causes	90	Prevalence 17%	Preoperative, 3 weeks and 4 months postoperative	Preoperative remote pain, early postoperative pain intensity	2b	[21]
Gerbershagen *et al.* (2009)	Nephrectomy for benign and malignant causes	35	Incidence 3 months: 29%; 6 months: 9%	Preoperative, 3 and 6 months postoperative	Preoperative pain intensity, anxiety, reduced physical health, number of co-morbid conditions and related disability, early postoperative pain intensity	2b	[22]
Bisgaard *et al.* (2005)	Laparoscopic cholecystectomy	150	Incidence 5%	Preoperative, 1 year postoperative	Early postoperative pain intensity	2b	[23]
Brandsborg *et al.* (2007)	Hysterectomy for benign causes	1173	Prevalence 31.9%	1 year postoperative	Preoperative pain, previous cesarean delivery, pain as main indication for surgery	4	[24]
Gerbershagen *et al.* (2009)	Radical prostatectomy	84	Incidence 3 months: 14%; 6 months: 1.2%	Preoperative, 3 months and 6 months postoperative	Preoperative pain, psychosomatic symptoms and worse mental functioning	2b	[9]
Kolesnikov *et al.* (2013)	Radical prostatectomy and hysterectomy	102	Prevalence: 34.3%	3 months postoperative	No association between catechol-*O*-methyl transferase polymorphisms and chronic postsurgical pain	2b	[16]
Peters *et al.* (2007)	General surgery	625	Incidence 12.5%	Preoperative, acute and 6 months postoperative	Acute postoperative pain, pain expectation, fear of consequences of surgery and duration of surgery	2b	[25]

• Psychological factors

Psychological vulnerability, often assessed in terms of depression, anxiety and pain catastrophizing, is frequently reported as a risk factor for CPSP development [1,19,25,28]. Patients reporting CPSAPP more often suffered from preoperative depressive symptoms [3,19,29] and pre- and postoperative anxiety [3,19–20,22]. Results on pain catastrophizing were less consistent; it emerged as a risk factor for chronic pain after gynecologic [19–20], but not after thoracic [30] and general surgery [25]. In laparoscopic cholecystectomy, pain catastrophizing was only related to acute and not to CPSP [23].

After regression analysis of psychological risk factors, emotions in response to the underlying illness emerged as the strongest predictor in hysterectomy patients (OR: 1.73; 95% CI: 1.2–2.5) [20]. Whether anxiety, depression and catastrophizing should be seen as three separate entities is debatable. Pinto *et al.* reported a moderate correlation between anxiety and pain catastrophizing (rho = 0.56) [20].

Nocebo effect

A psychological phenomenon receiving increased attention in chronic pain development is the nocebo effect. Contrary to the placebo effect, the nocebo induces negative effects due to negative expectations [31]. In a recent study in healthy volunteers, negative expectations of mechanical pain stimuli led to increased pain scores [32]. Similar results were shown for itch induced by somatosensory stimuli [31], and the nocebo effect has been documented in clinical practice. In both abdominal and pelvic surgery, a high preoperative expectation of pain increased the risk of CPSAPP [3,20]. Fear of long-term consequences elevated the odds ratio (OR) of CPSP after general surgery to 1.9 (95% CI: 1.1–3.3) and was associated with poorer general recovery and QoL. Optimism improved general recovery and QoL, but did not affect pain scores [25].

• Genetic predisposition

A rising field of interest in pain research is the role of genetic factors in chronic pain. Though to date, few data are available, genetic polymorphisms, such as GTP cyclohydrolase enzyme, potassium channel subunit and the catechol-O-methyl transferase gene polymorphisms, were related to different types of chronic pain [16,33]. In lower abdominal surgery, the combination of various catechol-O-methyl transferase and opioid receptor μ-1 polymorphisms was associated with an 18% decrease in morphine dosage in the first 48 postoperative hours. In the same study, however, there was no association with CPSP [16].

• Pain processing

A few research groups studied abnormalities in central pain processing as possible predictor of acute and CPSP in general in the past decade [5,23,34–37]. Noninvasive techniques such as quantitative sensory testing (QST) and conditioned pain modulation (CPM) are means to assess central pain processing. QST provides information on sensory function at the peripheral and central level of the nervous system by measuring pain thresholds to different external stimuli of controlled intensity. CPM is a paradigm testing the ability to generate descending inhibitory pain modulation [38,39].

Several studies found a correlation between preoperative sensitivity to experimentally induced pain and acute postoperative pain intensity [35–37]. In a cohort of 150 patients undergoing laparoscopic cholecystectomy, patients sensitive to a preoperative cold pressor test reported more acute postoperative pain, compared with patients more tolerant to this test [35]. At 6-month follow-up, no correlation was found with chronic postoperative pain [23]. In inguinal hernia repair, preoperative sensitivity to tonic heat stimulation was a significant predictor of CPSP [34]. Stronger central pain inhibition as assessed by CPM negatively correlated with the development of CPSP after thoracotomy (OR: 0.52; 95% CI: 0.33–0.77) [40]. A pilot study in major abdominal surgery reproduced the latter results, and demonstrated that spread and persistence of deep tissue hyperalgesia as a sign of central sensitization, correlated with chronic pain development [5].

• Preoperative pain

Preexisting pain, either at the surgical site or at remote sites of the body, seems to pose a major risk for developing CPSAPP [3,19–21,24]. Six months after gastrointestinal surgery, 35 and 29% of patients with surgical site and/or remotely located preoperative pain reported CPSP compared with only 3% of patients without preoperative pain [3]. Regarding hysterectomy, preoperative abdominopelvic pain tripled the odds of persistent pain [19,24]. Contradictory

results were reported by Peters *et al.*, who found less CPSP after general surgery in patients with preoperative pain (OR: 0.32; 95% CI: 0.17–0.60) [25]. However, this study did not specify for abdominal or pelvic surgery, and defined CPSP as merely an increase of pain after surgery.

The preoperative use of opioids was related to more CPSAPP after gynecologic surgery (OR: 2.1; 95% CI: 1.3–3.5) [19] and predicted a worse outcome of thoracoscopic splanchnicectomy in chronic pancreatitis [41]. Furthermore, it is known that chronic opioid exposure in general can lead to opioid-induced hyperalgesia, and thus worsen pain perception [42].

Several conditions associated with chronic pain such as fibromyalgia, irritable bowel syndrome and Raynaud phenomenon have been associated with the development of persistent pain after surgery, but convincing evidence is scarce [6,43].

• Surgical procedure

Location, duration, surgical approach and amount of nerve and tissue damage are thought to play a key role in CPSAPP development. Patients undergoing colorectal surgery were less likely to develop chronic pain than patients undergoing surgery of the upper gastrointestinal tract and hepatopancreaticobiliary system (OR: 0.46; 95% CI: 0.21–1.0) [10]. Similarly, in a study of 20 patients undergoing abdominal surgery, the group that reported chronic pain afterwards predominantly consisted of patients with upper gastrointestinal or genitourinary surgery [5]. The duration of a procedure extending 3 hours increased the OR of developing CPSP to 2.0 (95% CI: 1.01–3.97) in general surgery [25]. Whether this was attributable to the surgery itself or to the more complex underlying pathology is unknown [25]. In hysterectomy and nephrectomy, no relation between CPSP and operation time or blood loss was found [19,22].

Literature on the surgical approach and the development of CPSAPP is inconsistent. A survey of 124 patients after open (n = 56) and laparoscopic (n = 68) cholecystectomy revealed no differences in development of CPSP between groups [44]. A retrospective study comparing 155 patients after open cholecystectomy to 205 patients after laparoscopic cholecystectomy reported significantly more upper right quadrant pain after the open approach [45].

Hysterectomy via a vertical abdominal or Pfannenstiel incision was significantly more associated with the occurrence of persistent pain 4 months after surgery than via the vaginal route or laparoscopic hysterectomy [20]. Others found that the surgical approach did not affect the prevalence of CPSAPP [15,19,26], although a trend toward less persistent pain after a vaginal hysterectomy was seen (OR: 0.70; 95% CI: 0.46–1.06) [24].

The presence of numbness after Pfannenstiel incision, and repeated (>2) Pfannenstiel incisions independently increased the OR for chronic pain at the incision site to 3.01 (95% CI: 2.05–4.40) and 2.92 (95% CI: 1.44–5.93), respectively [46]. Emergency compared with elective cesarean delivery also proved a significant risk factor for chronification of postoperative pain (OR: 1.56; 95% CI: 1.01–2.40) [46].

• Early postoperative pain

Early postoperative pain intensity is regularly reported as a significant risk factor for persistent postoperative pain [1,6,9,19,23,25,43,47–48]. A cohort of 625 patients undergoing elective abdominal and nonabdominal, e.g., thorax, back and extremity surgery, showed a threefold increase of odds for developing CPSP in patients with a higher early postoperative pain intensity (OR: 3.21; 95% CI: 1.6–6.3) [25]. Similar results were found for moderate and severe pain after gynecologic surgery (RR: 3.0; 95% CI: 1.0–9.4) [19]. Pinto *et al.* reported pain frequency rather than intensity as a predictor (OR: 2.25; 95% CI: 1.04–4.9) [20].

Also after laparoscopic cholecystectomy, patients with chronic postoperative pain had suffered from significantly more intense early postoperative pain [23]. In major abdominal surgery, patients with moderate and severe early postoperative pain reported CPSP almost three-times more often than patients with no or mild pain. However, risk factor analysis did not identify early postoperative pain as a significant predictor [3]. Women with chronic pain after hysterectomy more often had postoperative complications compared with pain-free patients [24].

• Perioperative analgesia

Type of anesthesia may play a protective role in CPSAPP development by decreasing acute postoperative pain, as well as by blocking the transmission of perioperative noxious signals

to the spinal cord, minimizing alterations in central pain processing [49–51].

A recent Cochrane meta-analysis on pharmacotherapy in general surgery found a modest reduction in CPSP incidence for the NMDA antagonist ketamine (Risk ratio: 0.65; 95% CI: 0.47–0.83). No effect was found for the centrally acting Ca^{2+}-channel blockers gabapentin or pregabalin. Ketamine also proved effective in chronic abdominal and pelvic pain prevention, based on the results of four studies (Relative risk [RR]: 0.40; 95% CI: 0.19–0.88) [52].

Epidural anesthesia prevented CPSP in one out of four patients after thoracotomy and in one out of five women after breast surgery [53]. For major digestive surgery, epidural administration of analgesics resulted in less chronic pain at 6- and 12-month follow-up, and intraoperative use of the epidural proved superior to only postoperative use [54]. In nephrectomy [22] and gynecological surgery, however [21,55], the addition of epidural analgesia to general anesthesia did not reduce the prevalence of CPSAPP. Literature is inconsistent on the effect of spinal versus general anesthesia in hysterectomy [19,24].

• Summary of risk factors

Largely consistent with literature of other surgical procedures [1–2,6,8,25,43], risk factors for CPSAPP include female gender, younger age, co-morbidities, preoperative pain, early postoperative pain, altered central pain processing and psychological factors such as depression, anxiety and pain catastrophizing. Worse disease-related cognitions and emotions as well as worse expectations regarding postoperative pain also are related to an increased risk of developing CPSAPP **(Table 1)** [3,9–10,19–22,24]. In addition, several analgesic regimens protect against CPSAPP development [52,54].

Among these factors, preoperative pain emerged as the strongest predictor of CPSAPP after regression analysis in multiple trials, approximately leading to a threefold increase of odds for developing CPSAPP [3,19,24]. Other strong risk factors are younger age [10,20], female gender [3,10], acute postoperative pain [19,25] and psychosocial factors [3,19–20,25].

Comments

Current studies on CPSAPP show considerable variation in duration of follow-up, type of risk factors assessed and not least important, in definition of CPSAPP. Often, it is not mentioned whether the pain was a continuation of preoperative pain and if other causes for pain were excluded. Furthermore, timing of assessments differs greatly and though most studies are prospectively executed, it is not clearly stated whether incidence or prevalence is reported. Therefore, the mentioned risk factors can only be seen as associated factors in some cases and as predictors in others. Detailed data on the possibly most important risk factor 'preoperative pain' often are lacking, and protective factors are neglected. Also, in some analyses, CPSP is only considered present in case of moderate to severe pain, whereas in other studies any pain or discomfort is used.

These inconsistencies in study design and definition probably contribute to the large differences in outcomes between studies, and make the interpretation of risk factors more difficult.

CPSP is a multifactorial phenomenon. Contributing factors often cannot be seen as separate entities and many factors may influence each other, which must be taken into consideration when assessing them.

Apart from surgical tissue damage and inflammation, nerve injury is often mentioned as an important factor in CPSP development, and surgical procedures highly associated with nerve damage, such as limb amputations and posterolateral thoracotomies, depict the highest incidence of CPSP. As hyperalgesia due to inflammation and tissue damage usually subsides after wound healing, it is thought that sensitization as a result of nerve injury often persists due to long lasting or permanent damage [26]. Avoiding nerve damage could therefore lower the incidence of CPSP [2,29,33]. Estimated numbers of neuropathic pain after abdominal and pelvic procedures vary between 13.5% [10], 17.1% [16] and 30% [21]. These numbers suggest that neuropathic pain after abdominal and pelvic surgery exists, but may not be responsible for the majority of cases with CPSAPP [17]. However, neuropathic pain is a difficult diagnosis, and one may question whether abdominal neuropathic pain is comparable to other neuropathic pain, as viscera are projected via autonomic nerve fibers [56].

Other than intraoperative nerve damage, the entrapment of nerves in scar tissue is suggested as a possible source of pain. Of 690 women

undergoing hysterectomy via Pfannenstiel incision, 32% reported chronic pain at the incision site 2 years after surgery. Entrapment of the iliohypogastric or ilioinguinal nerve was found in over 50% of these patients with moderate to severe chronic pain [46].

Another often debated cause of chronic pain after abdominal and pelvic surgery is the formation of intra-abdominal adhesions [14,57]. According to a recent meta-analysis, adhesions were identified by laparoscopy as the most likely cause of pain in 57% of patients suffering from CPSAPP [57]. Some procedures, such as colectomies, hysterectomies and ovarian surgery, lead to more adhesion formation than others, especially in combination with radiotherapy [58–61]. Results on adhesiolysis for pain relief are inconsistent, but most studies did not incorporate the use of adhesion barriers [62–65]. As adhesion barriers have shown the ability to reduce the reformation and clinically relevant consequences of adhesions [66], its standard use can possibly prevent a substantial amount of CPSAPP cases.

• Prediction & prevention

A major goal of identifying risk factors for CPSAPP is to translate these into a reliable prediction model in order to estimate an individual's susceptibility to CPSAPP.

Once a clear prediction model is established, screening methods can be implemented preoperatively and preventive measures for patients at risk can be taken. As mentioned before, there is evidence suggesting an association between preoperative abnormalities in central pain processing and CPSAPP [5]. Notably, QST has recently shown to be of predictive value for pain reduction after pregabalin treatment in chronic pancreatitis pain [67].

While not yet part of current preoperative evaluation, screening QST and CPM might help to select patients at risk of CPSAPP and their value should be further investigated [68].

Risk factors for early postoperative pain greatly overlap with CPSAPP risk factors [69]. As it is uncertain whether early postoperative pain is the result of intraoperative injury and inadequate pain management, or a predisposition to pain, the relation to CPSP is difficult to determine [22]. Nonetheless, reducing acute postoperative pain and reducing the magnitude of intraoperative injury seems an important step in preventing CPSAPP. Larger, well-established trials are needed to confirm effectiveness of preventive analgesia for implementation in standard perioperative care.

Considering the contribution of psychological factors to CPSAPP, the preoperative screening and adequate counseling of psychological factors such as depression, anxiety, pain catastrophizing and negative expectations and cognitions, may have a significant impact on reducing the incidence of CPSAPP.

• Future perspective

In order to obtain reliable epidemiologic data on risk factors for CPSAPP, it is important that larger future studies are conducted in a prospective and more standardized way. In a recent systematic review, VanDenKerkhof *et al.* propose a core set of outcomes including demographics, pain scores and characteristics, clinical factors, surgery-related factors and data on psychological and physiological functioning for future research on CPSP risk factors. Also, tools and timing for assessment of these outcomes were proposed [70]. In our opinion, the pre- and postoperative assessment of central pain processing is a relevant addition to this core dataset. Conducting logistic regression models obtaining hierarchy in the importance of the established risk factors [20] is an important step in the development and validation of a prediction model of CPSP.

Conclusion

Chronic pain is a significant negative consequence of abdominal and pelvic surgery and several factors contribute to its development. Establishing a prediction model based on known risk factors to identify susceptible patients and applying protective measures is an important step toward preventive, personalized health care.

Financial & competing interests disclosure

The authors are supported by their university medical center. They are also supported by a grant of the European Union, the European Fund for Regional Development (EFRO, 'Here is an investment in your future'). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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