

# **Prevalence and predictors of persistent postsurgical pain 12 months after thoracotomy**

**Authors:** Fredrik Hetmann, Ulf E. Kongsgaard, Leiv Sandvik, Inger Schou-Bredal

**Location:** Oslo University Hospital, Oslo, Norway

**Short Title:** Persistent postsurgical pain

**Word Count:** 2 998

## **Correspondence:**

Fredrik Hetmann

Assistant Professor/PhD student

Oslo and Akershus University College of Applied Sciences

Faculty of Health Sciences

*Department of Nursing*

PB 4, St.Olavs plass, N-0130 Oslo, Norway

Telephone: + 47 93 22 42 71

Fax: N/A

e-mail address: [fredrik@hetmann.no](mailto:fredrik@hetmann.no)

## **ABSTRACT**

**Background:** Persistent postsurgical pain is recognised as a major problem. Prevalence after different surgical procedures has been reported to range from 5% up to 85%. Limb amputation and thoracotomy have the highest reported prevalence. Prediction of persistent postsurgical pain has over the last decade caught attention. Several factors have been investigated, but in-depth knowledge is still scarce. The purpose of this study was to investigate the prevalence of persistent postsurgical pain, and predictive factors for persistent postsurgical pain 12 months after thoracotomy.

**Methods:** A prospective longitudinal study was conducted. One hundred and seventy patients were recruited before scheduled thoracotomy, and asked to answer a questionnaire. One hundred and six patients completed the same questionnaire at 12-month follow-up. Regression analysis was performed to explore variables assumed predictive of persistent postsurgical pain.

**Results:** One-hundred and six patients (62%) filled out the questionnaire at both time points. Preoperative, 34% reported muscle-skeletal related chronic pain. At 12-month follow-up 50% of the patients reported persistent postsurgical pain. Of the variables explored in the logistic regression model, only preoperative pain ( $p<0.001$ ) and dispositional optimism ( $p=0.04$ ) were statistically significant. In this study preoperative pain was a predominant predictor for persistent postoperative pain (OR 6.97, C.I. 2.40-20.21), while dispositional optimism (OR 0.36, C.I. 0.14-0.96) seem to have protective properties.

**Conclusion:** Our results show that preoperative pain is a predominant predictor of future pain. This implies that patients presenting with a chronic pain condition prior to surgery should be assessed thoroughly preoperatively and have an individually tailored analgesic regimen.

**Key words:** Pain – Preoperative pain– Persistent Pain – Thoracotomy – Thoracic surgery

## INTRODUCTION

Persistent pain after surgery is considered a major health problem influencing a large number of patients. Most surgical procedures carry a risk of persistent pain, which may last for months and/or years. The consequences are to varying degrees disabling both physically and mentally for many patients, and represents an economically challenge to public health.<sup>1</sup> Depending on type of surgery, prevalence has been reported to range from 5 % up to 85 %.<sup>1-3</sup> Limb amputation and thoracotomy are two of the surgical procedures with the highest reported prevalence.

The International Association for the Study of Pain (IASP) has defined Post-Thoracotomy Pain Syndrome (PTPS) as pain persisting more than 2 months after thoracotomy.<sup>4</sup> Persistent postsurgical pain, abbreviated PPSP, has emerged as a term in literature over the last decade. Werner and Kongsgaard<sup>5</sup> have recently proposed a new set of criteria for PPSP in order to differentiate PPSP from other non-surgical related pain states. PPSP is probably a more precise way of expressing the prolonged period from acute postoperative pain, to pain persisting beyond time perceived as acceptable.<sup>2,5,6</sup>

Recent studies have focused on predictive factors of persistent pain following thoracic surgery.<sup>7</sup> Knowledge regarding which patients are at risk remains crucial, in order to develop preventive interventions. A body of literature has identified several factors, independent of surgical procedure, believed to contribute in the transition from early postoperative pain to persistent postsurgical pain.<sup>7</sup> Preoperative factors (such as age, sex, genetic susceptibility, psychosocial factors and presence of pain before surgery), intraoperative factors (such as type of surgery, open vs. endoscopic, type of analgesia) and lastly postoperative factors (such as level of postoperative acute pain) have all been set forth as important predictive factors.<sup>8-14</sup> It has also been postulated that properties of the brain's circuitry may be predictive of chronic pain.<sup>15</sup> However, these findings are inconclusive due to the lack of a comprehensive approach.

A flaw in many epidemiological studies is the lack of preoperative information about the patients.<sup>7</sup> To our knowledge, no study to date has investigated comprehensively all factors predicting PPSP following thoracic surgery in the sense of investigating all before mentioned factors simultaneously. The objective of this study was:

1) To identify the prevalence of persistent pain after 12 months.

2) To identify predictive factors for persistent pain 12 months after thoracotomy.

## MATERIALS AND METHODS

A prospective study was conducted from December 2007 through August 2010. One hundred and seventy patients scheduled for lung surgery via thoracotomy admitted to the Thoracic Surgical Department of Oslo University Hospital were recruited. Inclusion criteria were patients over 18 years old, able to speak and write Norwegian, and give their written informed consent. Exclusion criteria were cognitive impairment or physical inability to fill out a questionnaire. Approval was obtained in September 2007 from the Regional Committee for Medical Research Ethics in Eastern Norway, Oslo, Norway [REK no.420-07197a 1.2007.1165] and Social Science Data Services at Oslo University Hospital [no.849].

The day before surgery, participating patients completed a constructed study questionnaire providing information about demographic data, psychosocial factors and whether or not any preoperative pain condition was present. Patients reporting preoperative pain were asked to elaborate further about their pain condition.

A small group of experienced surgeons performed the thoracotomies using an open posterolateral technique. Thoracic epidural analgesia (TEA) was delivered as a continuous infusion of a commercially prepared (Standard EDA-blanding, Fresenius Kabi, Halden, Norway) triple drug mixture (bupivacaine 1mg/ml, fentanyl 2µg/ml and adrenaline 2µg/ml) via a thoracic epidural catheter inserted before surgery. TEA was weaned off on the 3<sup>ed</sup> or 4<sup>th</sup> postoperative day. Paracetamol 1g was given routinely every 6h. Breakthrough pain was treated with intravenously ketobemidone (Ketorax, Pfizer, Lysaker, Norway).

Verbal Numeric Rating Scale (V-NRS) was used to assess pain at rest and provoked pain by cough or deep breaths, for six consecutive days after the surgery, or as long as the patients were hospitalised. V-NRS ranges from 0 being *No Pain* to 10 being *Worst Pain Possible*. Pain scores  $\geq 4$  was considered clinically important for treatment.<sup>16</sup>

The questionnaires used at baseline and 12 months were:

- The Brief Pain Inventory-Short Form (BPI), which has been translated into Norwegian and validated was utilized.<sup>17,18</sup> BPI is a general pain measurement tool consisting of 15 questions mapping pain localisation, -intensity, -treatment and impact on daily activities. The first question asks whether pain other than everyday kinds of pain (e.g. headaches, sprains or toothaches) is present or not. If the answer is yes on the first question, the rest of the

questionnaire is completed. Question 2 consists of a front and back body map, where the purpose is to mark the localisation(s) of the pain. Four questions ask about pain severity (least, worst, average and current pain) on an 11-point scale from 0 (*no pain*) to 10 (*Pain as bad as you can imagine*). Two questions address pain treatment and its effect. The last seven questions address pain interference on everyday activities last 24h on an 11-point scale from 0 (*Does not interfere*) to 10 (*Completely interferes*).

- The Life Orientation Test-revised (LOT-R) was used to assess dispositional optimism.<sup>19</sup> LOT-R is a 10-item self-report scale (6 target items and 4 fillers), using a 5-point scale from 0 (Strongly disagree) to 4 (Strongly agree). A higher score indicates a more optimistic life orientation, and the time frame used is now. The form has been translated into Norwegian and validated.<sup>13</sup>
- The Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depression.<sup>20</sup> HADS is a self-reporting questionnaire consisting of 14 items, seven measuring anxiety and seven measuring depression. Each item is scored on a 4-point scale (0-3). A cut-off score of  $\geq 8$  gives a sensitivity and specificity for both sub-scales of approximately 0.80. The form has been translated into Norwegian and validated.<sup>21</sup>

At 12 months study questionnaires were sent by mail to all eligible patients (Fig.1). Before mailing the questionnaires, the National Registry was checked to avoid sending to deceased patients. In the present study, only patients who at 12 months both reported pain other than everyday kind of pain, and shaded on the body map an area corresponding to the surgical scar were categorised as having PPSP.

### ***Statistical analysis***

Predictive Analytics Software Statistics version 18 (SPSS Inc. Chicago, IL, USA) was used for all analyses. Only patients who had completed both questionnaires (baseline and 12 months) were included in the analyses. General descriptive statistics, frequencies, means and standard deviations were utilised. Univariate logistic regression was conducted to assess each variable separately as a predictor for persistent postsurgical pain. The variables

assessed were age, gender, preoperative pain, body categories, dispositional optimism, emotional distress and postoperative pain. We defined postoperative pain as average pain score from day 0 to day 5. As suggested by Hosmer and Lemeshow, we included in the multivariate logistic regression all variables from the univariate analyses with a p-value  $\leq 0.25$ .<sup>22</sup> For the multivariate logistic regression we performed a backward variable selection. The Hosmer-Lemeshow goodness-of-fit test was applied on the final model, in which  $P > 0.05$  indicated support for the model. The significance was set at 5 %. The Hosmer-Lemeshow goodness-of-fit test was nonsignificant with  $P = 0.67$ .

## RESULTS

Of 170 patients, 106 (62 %) filled out the questionnaires both at baseline and 12 month follow-up. Twenty-seven (16%) patients died before the 12 month follow-up and 37 (22%) patients did not respond to the questionnaires mailed to them (fig.1). There was no significant difference in baseline characteristics between the patients responding at 12 months and those not responding. No patients were excluded.

### *Baseline*

Out of 106 patients 59 (56 %) were men and the mean age was 65 years. Forty-four (27 %) of the patients had more than 12 years of education. Table 1 presents baseline characteristics.

At baseline, 36 (34 %) patients reported having preoperative pain not associated with their current diagnosis. Most frequently reported origins of pain was neck/shoulder, lower back, hips or knees. Half of these patients stated pain from more than 3 body regions. From the BPI items, 23 (30 %) of the patients rated their average pain last 24 hours to be moderate to severe. Least pain last 24 hours was reported to be moderate to severe by 3 (4 %) patients. Table 2 presents pain characteristics and interference.

The total mean score for Dispositional optimism was 16.3( $\pm$ 3.81). With a cut-off of 16, 40 (47 %) of the patients were identified as optimists. When comparing patients with and without preoperative pain, there was no significant difference (*t-test*) regarding Dispositional optimism.

Anxiety was present with 20 (22 %) of the patients and depression present with 4 (4 %). Five patients (5 %) reported both anxiety and depression. For anxiety, the mean score for patients without preoperative pain was 4.95( $\pm$ 3.46) and 8.12( $\pm$ 4.81) for those with preoperative pain. This was statistically significant with  $p < 0.001$ . For depression, those without preoperative pain had a mean score of 3.03( $\pm$ 2.78) and 4.47( $\pm$ 3.47) for those with preoperative pain. This was also statistically significant with  $p = 0.03$ .

### *12-month follow-up*

Fifty-three (50 %) patients could be categorised as having PPSP. From the BPI items, 15 (15 %) patients rated their average pain last 24h to be moderate to severe. Least pain last 24 hours was reported to be moderate to severe by 7 (7 %) patients. At 12 months moderate to severe pain interference was also most predominant with Normal Work, Walking Ability and General Activity (Table 2).

### *Logistic regression*

Age, gender, preoperative pain, body categories, dispositional optimism, emotional distress and postoperative pain were all included in the univariate analyses (table 3). A  $p$ -value  $> 0.25$ , excluded both body categories ( $p=0.8$ ) and emotional distress ( $p=0.28$ ). For the multivariate regression model, age, gender, preoperative pain, dispositional optimism and postoperative pain were included. During the backward variable selection age, gender and postoperative pain were excluded. This left only the variables preoperative pain ( $p < 0.001$ , OR=6.97) and dispositional optimism ( $p=0.04$ , OR=0.36) as statistically significant (table 3).

## DISCUSSION

### *Prevalence of persistent postsurgical pain*

In our study, 50% of the patients reported persistent postsurgical pain one year after surgery. Other studies of pain after thoracotomy, have reported ranges from 5 % to 65 %.<sup>1-3,23</sup> In comparison to previous reported range, our result is in the upper end for this type of surgery.

At baseline, prior to surgery, the prevalence of preoperative pain was 34 %. Two studies have reported the prevalence of chronic pain in the Norwegian general population to be 25-30%.<sup>24,25</sup> Compared to other European countries, which had prevalence between 10 and 20 %, Norway had a 10 % higher prevalence. Our results are in accordance with the general population. We have no good explanation why Norway stands out in this respect, and to our knowledge, no studies have investigated the underlying causes behind the high number of Norwegians reporting chronic pain. Data from the Norwegian Institute of Public Health underpins the notion that a major cause to chronic pain is muscle and skeleton related and caused by e.g. manual labour or static work. This was also the predominantly reported cause among patients with preoperative pain, in the present study. Chronic pain conditions affect women more than men, are more common in relation to low income and education, and are increasingly common with growing age.<sup>26</sup> Some of our findings in this respect are consistent with these data. We found that most of our respondents were close to or above the age of retirement (67 years). Only 25 % had completed more than 12 years of education, which may imply that the majority of the respondents would be placed in the low income and education group. Regarding gender, more than half of the respondents were males. The main reason for surgery were lung cancer and according to statistics from the Cancer Registry of Norway 15 % more males than women were diagnosed with lung cancer in 2011.<sup>27</sup> Thus, reflecting more men participating in this study.

### *Predictors of persistent postsurgical pain*

There has been great emphasis over the last decade trying to understand the mechanisms behind pain persisting beyond expected time course after surgery. What research has shown, is how multi-faceted this field of research is and difficult to fully comprehend.<sup>1-3,28,29</sup> Numerous factors have been proposed as predictive of persistent postsurgical pain. VanDenKerkhof and colleagues have proposed a framework in epidemiological studies, allowing for better ways of comparing studies.<sup>7</sup> In our study, we incorporated known risk factors and used validated instruments to measure these factors. Seven variables (age, gender, preoperative pain, body categories, dispositional optimism, emotional distress and postoperative pain) were explored in the regression model. From the multivariate analysis, preoperative pain and dispositional optimism were factors predictive of persistent postsurgical pain. The odds of experiencing persistent pain were almost seven times when having a preoperative pain condition before surgery. This is in accordance with several reports stating that preoperative chronic pain being a strong predictor for persistent postsurgical pain.<sup>2,3,30</sup> To date, research has not been able to fully explain why “pain predicts pain”.<sup>28</sup> Protracted exposure to nociceptive input by chronic pain, may contribute to central sensitization. Surgical incision, subsequent tissue injury, inflammatory processes, pathophysiological responses and genetic susceptibility may lead to amplification of preoperative pain.<sup>2,28</sup> A recent study by Johansen and colleagues<sup>31</sup> found results similar to ours. Preoperative pain was a major contributor in patients reporting PPSP and moderate to severe pain from the surgical area were experienced by about 18 %.

The intensity of acute postoperative pain is believed to be associated with pain persisting beyond the immediate postoperative period. However, some earlier studies supporting this view, have methodological weaknesses e.g. retrospective design and small sample sizes.<sup>7</sup> Contrary to previous reports on acute pain levels, none of our responders reported acute postoperative pain levels above mild (NRS <3) at rest or NRS above four with provoked pain in our study. One possible explanation could be that all patients postoperatively received thoracic epidural analgesia (TEA) using a triple drug mixture (bupivacaine, fentanyl and adrenalin). In a previous article, we set forth the question whether the TEA had the ability to alter the pain response or if it was just masking the pain response.<sup>32</sup> From the results found

in this present study, it is highly probable that the TEA only has the ability to mask the pain response. Hence, underlying pain processes are not completely blocked.

In accordance with some studies, we also found that anxiety and depression were associated with chronic pain prior to surgery.<sup>14,33</sup> There may be a bi-directional aetiology – pain causing poor mental health and vice versa. There is an unclear relationship between mental health and chronic pain. Even though we did collect preoperative data regarding mental status, we did not record which came first, pain or anxiety/depression. Some patients may have had a long history of anxiety/depression, while other patients who have been living with chronic pain for years may have developed anxiety/depression.

In the present study, only dispositional optimism and preoperative pain were found to be predictors of PPSP at 12 months. Dispositional optimism has been described as a stable personality trait, recognised by a general expectation of future positive versus negative outcomes. Optimism seems to be protective against pain persisting after surgery. A plausible explanation for this could be that optimists may have less expectation of pain, and therefore less negatively affected by pain. In addition, dispositional optimism may lead to patients experiencing increased control and consequently use active strategies to cope when experiencing pain. Thus, adapting better when exposed to surgical pain. Whether more optimism results in less pain or vice versa, is yet to be established.<sup>9</sup> In our study, 47% of the patients were categorised as optimists. Our results show that optimism may have a protective influence regarding persistent postsurgical pain.

Preoperative pain was the strongest predictor for PPSP at 12 months after thoracotomy. Contrary to a cross-sectional study design, prospective longitudinal design has made for a thorough evaluation of the correlation between the variables under study and PPSP. Our results have implications for clinical practice. Patients scheduled for surgery with a preoperative pain condition, poses a challenge to clinicians. Pain being the strongest predictor of pain, implies that every patient with a chronic pain condition should have an individual preoperative assessment and tailored analgesic regimen in conjunction with planned surgery. The challenge, however, is that knowledge regarding which analgesic regime to choose is still scarce. For some patients a thorough assessment could lead to a well-tailored analgesic regimen, whilst for other patients it may be difficult to fully assess the underlying mechanisms of their chronic pain. Thus, making it difficult to tailor efficacious

analgesia. Kehlet and colleagues have also pointed out that surgeons play an important role in preventing PPSP.<sup>6</sup> Choosing surgical techniques that minimize the impact on soft tissue, muscles and nerves may prevent persisting pain in some patients. However, there are still gaps in the literature regarding this problem area.

### *Strengths and limitations*

One strength of this present study is its prospective design with a 12-month follow-up. Possible predictive factors was investigated simultaneously, as suggested by VanDenKerkhof and colleagues<sup>7</sup>. Furthermore, only validated instruments such as the BPI, HADS and LOT-R were used to collect data. The final model was tested using the Hosmer-Lemeshow goodness-of-fit test, its results supports the model. A limitation is that the patients in this study reflect the Norwegian population and this does not necessarily make the results transferable to a general population. It could be argued that a response rate of 62% is a limitation for this study. The baseline characteristics for the patients not responding at 12 months (either dead or non-responders) did not differ from the patients in the active data set. However, we cannot insure that our findings would have been identical if the non-responders had answered the questionnaires.

### *Conclusion*

PPSP pain was prevalent in 50% of the patients participating in this prospective single-centre study. Preoperative pain increases the risk of PPSP if preoperative pain is present. This adds to earlier research claiming that pain predicts pain. Future research should focus further on the role of existing chronic pain in conjunction with surgery and its role in PPSP.

## Acknowledgments

Funding was received from Division of Emergencies and Critical Care, Oslo University Hospital, Norway

and

Oslo and Akershus University College of Applied Sciences, Faculty of Health Sciences, Department of Nursing

Conflicts of interest: The authors have no conflicts of interest.

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Figure legend:

**Figure 1:** Flow chart of the patient inclusion and reasons for exclusion in a prospective longitudinal study of prevalence and predictive factors for persistent pain 12 months after thoracotomy, Oslo University Hospital, Norway (Dec 2007-Aug 2010).

**TABLE 1**

Baseline characteristics (n=106)

Age, mean (SD)	65.16(11.00)
Gender <i>n</i> (%)	
female	47(44)
male	59(56)
Education >12 years <i>n</i> (%)	44(27)
Dispositional optimism <sup>†</sup>	
mean (SD)	16.30(3.81)
optimist <i>n</i> (%)	40(47)
Emotional distress <sup>‡</sup> <i>n</i> (%)	
anxiety	20(22)
depression	4(4)
both anxiety and depression	5(5)

<sup>†</sup> LOT-R: cut-off ≥16, higher score indicating more optimism<sup>‡</sup> HADS: cut-off ≥8 for both sub-scales

**TABLE 2**

Pain characteristics and interference at baseline and 12 month follow-up (n=106)

Baseline					12 month follow-up			
Preoperative pain 36(34%) More than 3 painful body regions 20(51%)					Persistent postsurgical pain 53(50%)  N/A			
BPI items <sup>a</sup>	No pain (NRS 0)	Mild pain (NRS 1-3)	Moderate pain (NRS 4-6)	Severe pain (NRS 7-10)	No pain (NRS 0)	Mild pain (NRS 1-3)	Moderate pain (NRS 4-6)	Severe pain (NRS 7-10)
Worst pain last 24h	38(51%)	20(27%)	15(20%)	2(3%)	42(43%)	36(37%)	14(14%)	6(6%)
Least pain last 24h	50(65%)	24(31%)	2(3%)	1(1%)	56(59%)	32(34%)	6(6%)	1(1%)
Average pain last 24h	34(46%)	18(24%)	22(29%)	1(1%)	40(41%)	43(44%)	11(11%)	4(4%)
Current pain	52(68%)	17(22%)	7(9%)	1(1%)	53(54%)	33(34%)	11(11%)	1(1%)
Pain interference last 24h with:	No interference (NRS 0)	Little interference (NRS 1-3)	Moderate interference (NRS 4-6)	Severe interference (NRS 7-10)	No interference (NRS 0)	Little interference (NRS 1-3)	Moderate interference (NRS 4-6)	Severe interference (NRS 7-10)
General Activity	33(52%)	16(25%)	11(18%)	3(5%)	59(60%)	20(21%)	14(14%)	5(5%)
Mood	41(57%)	17(24%)	9(12%)	5(7%)	63(65%)	22(23%)	11(11%)	1(1%)
Walking Ability	44(59%)	13(17%)	10(13%)	8(11%)	61(63%)	17(17%)	13(13%)	7(7%)
Normal Work	37(50%)	17(23%)	13(18%)	7(9%)	45(47%)	24(25%)	16(17%)	11(11%)
Relations with other people	46(62%)	18(25%)	6(8%)	4(5%)	72(74%)	19(19%)	5(5%)	2(2%)
Sleep	42(58%)	17(23%)	10(14%)	4(5%)	55(56%)	26(27%)	11(11%)	6(6%)
Enjoyment of life	41(55%)	22(30%)	5(7%)	6(8%)	55(56%)	29(30%)	9(9%)	5(5%)

<sup>a</sup>The Brief Pain Inventory-Short Form(BPI)

Baseline was prior to surgery. Only patients stating preoperative pain were asked to complete the BPI items, which is related to pain severity and interference. No pain and interference represents patients without preoperative pain.

At 12-month follow-up, those who both stated persistent pain and marked the area corresponding to the surgical scar were categorised as having PPSP. These patients were asked to complete the BPI items. No pain and interference represents patients not categorised as having PPSP.

**TABLE 3**

Results from the Logistic regression

	Univariate analysis				Multivariate analysis				Backward variable selection			
	<i>p</i>	OR	95% C.I. for OR		<i>p</i>	OR	95% C.I. for OR		<i>p</i>	OR	95% C.I. for OR	
			Lower	Upper			Lower	Upper			Lower	Upper
Age	0.07	0.97	0.93	1.00	0.82	1.00	0.96	1.05				
Gender	0.08	0.50	0.23	1.09	0.89	1.08	0.37	3.16				
Preoperative pain	0.001	4.28	1.82	10.06	0.005	5.58	1.71	19.57	<0.001	6.97	2.40	20.21
Body Categories	0.80	0.83	0.21	3.38								
Dispositional optimism <sup>a</sup>	0.09	0.47	0.20	1.11	0.07	0.38	0.13	1.10	0.04	0.36	0.14	0.96
Emotional distress <sup>b</sup>	0.28	1.64	0.67	4.01								
Postoperative pain	0.02	1.43	1.05	1.95	0.16	1.33	0.90	1.97				

*Persistent postsurgical pain at 12 months was defined as Dependent variable for the logistic regression analyses*

<sup>a</sup>Dispositional optimism measured using LOT-R

<sup>b</sup>Emotional distress measured using HADS