Received: 10 September 2024 | Revised: 23 November 2024 | Accepted: 28 November 2024

DOI: 10.1002/ejp.4768

ORIGINAL ARTICLE

Preoperative susceptibility to developing secondary hyperalgesia is associated with post-thoracotomy pain at 2 months

Solenn Gousset[1] | **Maximilien Cappe**[2,3,4] | **Cedric Lenoir**[1] | **Arnaud Steyaert**[1,2] | **Patricia Lavand'homme**[1,2] | **André Mouraux**[1] | **Valérie Lacroix**[2,4] | **Emanuel N. van den Broeke**[1,5]

[1]Institute of Neuroscience (IoNS), UCLouvain, Brussels, Belgium

[2]Institute for Experimental and Clinical Research (IREC), UCLouvain, Brussels, Belgium

[3]Department of Anesthesiology, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium

[4]Department of Cardiovascular and Thoracic Surgery, Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium

[5]Health Psychology, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium

Correspondence
Emanuel N. van den Broeke, Health Psychology, Faculty of Psychology and Educational Sciences, KU Leuven, Tiensestraat 102, Leuven 3000, Belgium.
Email: emanuel.vandenbroeke@kuleuven.be

Funding information
Fonds de Recherche Clinique of UCLouvain; ESA-BJA, Grant/Award Number: BJA-ESAIC_GR_2020_EV; European Union's Horizon2020 Research and Innovation Program, Grant/Award Number: 848068

Abstract

Background: Identifying the subset of patients at risk for developing persistent pain after surgery is clinically important as they could benefit from targeted prevention measures. In this prospective study, we investigated if the preoperative assessment of the individual susceptibility to developing experimentally induced secondary hyperalgesia is associated with post-thoracotomy pain at 2 months.

Methods: Forty-one patients scheduled to undergo a posterolateral thoracotomy were recruited before surgery and followed prospectively for 2 months. The day before surgery, we experimentally induced secondary hyperalgesia at one of the two forearms and measured the change of perception to mechanical pinprick stimuli and the area of hyperalgesia. On postoperative Day 4, Day 15 and at the 2-month follow-up, patients were asked about their pain intensity at rest and during coughing and the area of secondary hyperalgesia around the scar as well as the change in perception to mechanical pinprick stimuli was measured.

Results: Of the 41 patients that were recruited only 20 could be analysed. Forty per cent reported pain at the 2-month follow-up. All of them reported cough-evoked pain and 10 per cent also reported pain at rest. A binary logistic regression model with both the magnitude and extent of experimentally induced secondary hyperalgesia was statistically significant (chi-squared = 12.439, $p = 0.002$, McFadden $R^2 = 0.462$) and showed excellent discriminative power (AUC = 0.938) for the presence or absence of cough-evoked pain at the 2 month follow-up.

Conclusion: Our findings indicate that the individual susceptibility to developing experimentally induced secondary hyperalgesia preoperatively may identify patients who are potentially vulnerable to develop persistent post-thoracotomy pain.

Solenn Gousset and Maximilien Cappe contributed equally to this work.

Significance: Our data suggests that preoperatively assessed experimentally induced secondary hyperalgesia displays excellent discriminative power for the presence or absence of cough-evoked pain 2 months after thoracotomy.

1 | INTRODUCTION

Persistent pain is frequent after thoracotomy, with a reported prevalence between 30% and 60% (Bayman & Brennan, 2014; Lim et al., 2022). Identifying the subset of patients at risk for persistent post-thoracotomy pain is clinically important, as they could benefit from targeted prevention measures.

Using a prospective design, Martinez et al. (2012) showed that patients who suffered from postsurgical neuropathic pain at 3 months had larger areas of incision-induced secondary hyperalgesia (increased pinprick sensitivity of the skin surrounding the incision) in the immediate postoperative period. Moreover, clinical studies have shown that analgesic protocols that reduce the area of incision-induced secondary hyperalgesia also reduce pain at 3 and 6 months (De Kock et al., 2001, 2005; Lavand'homme et al., 2005; Salengros et al., 2010). While other prospective studies did not find a relationship between the area of incision-induced secondary hyperalgesia and pain at 6 months (Momeni et al., 2010; Setälä et al., 2016), Momeni et al. (2010) reported that significantly more patients with pain at 6 months had mechanical hyperalgesia at postoperative Day 5. Taken together, the relationship between the size of the area of incision-induced secondary hyperalgesia and the development of persistent postsurgical pain remains unclear (Brennan & Kehlet, 2005).

Importantly, the aforementioned studies focused on incision-induced secondary hyperalgesia, which can be affected by several factors (e.g. extent of wound surgery, wound complications and analgesic treatment). Moreover, one would ideally need a preoperative measure to identify at-risk patients as early as possible.

Secondary hyperalgesia can be induced experimentally (Quesada et al., 2021) and a previous study found that the areas of experimentally heat-induced secondary hyperalgesia and incision-induced secondary hyperalgesia after gynaecology surgery moderately correlated (Dirks et al., 2002). This raises the intriguing question of whether inter-individual variations in the preoperative susceptibility to develop experimentally induced secondary hyperalgesia is associated with who will develop persistent postsurgical pain. To the best of our knowledge, no clinical studies have investigated this yet.

We have shown that noxious electrical cutaneous stimulation can induce secondary hyperalgesia (van den Broeke et al., 2016, 2019; van den Broeke & Mouraux, 2014). Electrical stimulation has the advantage that it can be applied in a highly standardized and well-controlled manner. By comparing different frequencies of electrical stimulation, we found that middle-frequency stimulation (MFS) induced maximal secondary hyperalgesia in healthy human volunteers (van den Broeke et al., 2019). A follow-up reliability study further showed that the area of MFS-induced secondary hyperalgesia is highly reliable (Cayrol et al., 2020).

The aim of this prospective cohort study was to investigate, in patients scheduled to undergo thoracotomy for the treatment of lung cancer, if the extent of MFS-induced secondary hyperalgesia before surgery is associated with the presence of pain at 2 months. The 2-month endpoint was chosen to avoid potential confounding of adjuvant treatments (e.g. chemotherapy) to the development of persistent pain (Yoon et al., 2020). We hypothesized that individuals who develop greater experimentally induced secondary hyperalgesia before surgery are more likely to have pain 2 months after surgery.

2 | MATERIALS AND METHODS

2.1 | Patients

The study was approved by the Comité d'Éthique Hospitalo-Facultaire Saint Luc—UCLouvain (B403201940443) and conducted according to the Declaration of Helsinki. The study was pre-registered on clinicaltrials.gov (NCT04220697).

We estimated that a total of 70 patients would be needed. The sample size calculation was based on a logistic regression analysis of a binary response variable (presence/absence of pain at 2 months) and a continuous, normally distributed variable (perceived pinprick intensity). With a sample of 70 patients, we would achieve a power of 0.70 at a 0.05 significance level to detect a change in the proportion of patients with persistent post-thoracotomy pain from the value of 30% at the mean of perceived pinprick intensity to 45% when the perceived pinprick intensity is increased to one standard deviation above the mean. This change corresponds to an odds ratio of 1.9.

Patients were recruited between January 2020 and December 2023 at the Department of Cardiovascular and Thoracic Surgery of the Cliniques Universitaires

Saint-Luc in Brussels, Belgium. Inclusion criteria were: (1) being between 18 and 80 years old, (2) being scheduled for a pulmonary anatomical lung resection by posterolateral thoracotomy to treat primary lung cancer and (3) being able to provide written informed consent. Exclusion criteria were: (1) evidence for a clinically significant alteration of the skin of the volar forearms, (2) being pregnant and (3) having a pacemaker or implanted cardiac defibrillator.

Figure 1 details the patient selection. At the end of the study period, 41 eligible patients were included. All patients signed an informed consent. Of those 41 patients, we had to exclude nine patients because of problems with data collection. Furthermore, seven patients were excluded because they did not tolerate the pain induced by the MFS stimulation and requested to withdraw. One patient was excluded because his surgery was rescheduled some months after the preoperative assessment. Finally, we were not able to do the 2-month follow-up in four patients. Therefore, the final analysis included 20 patients (12 males/8 females, mean (±SD) age: 65.6 years ±12.5, ranging from 81 to 39 years).

2.2 | Design

Figure 2a shows the study design. On the day prior to their surgery (D-1), patients were asked to fill out a set of questionnaires about the presence and impact of pain (brief pain inventory), whether this pain is of neuropathic origin (DN4) and about anxiety and depression (Hospital Anxiety and Depression Scale). After that, the mechanical pinprick sensitivity of the chest skin of the side that had to be operated was assessed. Then, the mechanical pinprick sensitivity of the skin at both forearms was assessed before and after MFS was applied to induce secondary hyperalgesia at one of the two forearms. The next day (D0) patients underwent surgery (thoracotomy). Four days after their surgery (D4), patients were asked about the intensity of their pain at rest and during coughing. Furthermore, the mechanical pinprick sensitivity around the scar was assessed (intensity of perception and area of secondary hyperalgesia). Those same assessments were repeated at 15 days (D15) and 2 months (M2) after surgery. At the 2-month follow-up, patients were also asked to fill out the same questionnaires as the ones on the day before surgery (D-1).

2.3 | MFS and the assessment of MFS-induced secondary hyperalgesia

2.3.1 | MFS

MFS was used to induce secondary hyperalgesia on the volar forearm skin. MFS consisted of 12 trains of 42 Hz biphasic charge-compensated electrical pulses (Cayrol et al., 2020; van den Broeke et al., 2019). Each biphasic pulse consisted of a 2-ms square-wave pulse followed, after a 0.1-ms delay, by a 4-ms compensation pulse of opposite polarity having half the intensity of the first pulse. Each train lasted 1 s and was delivered in a 10-s interval. The total duration of the stimulation protocol was 2 min.

MFS was applied to one of the two forearms approximately 10 cm from the cubital fossa. The arm at which

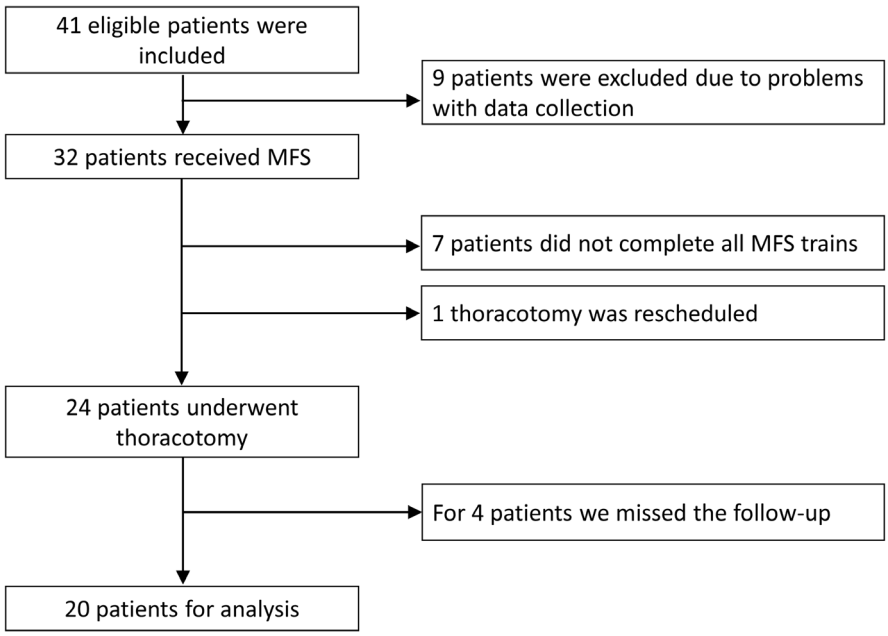

FIGURE 1 Flowchart of patient selection (see text).

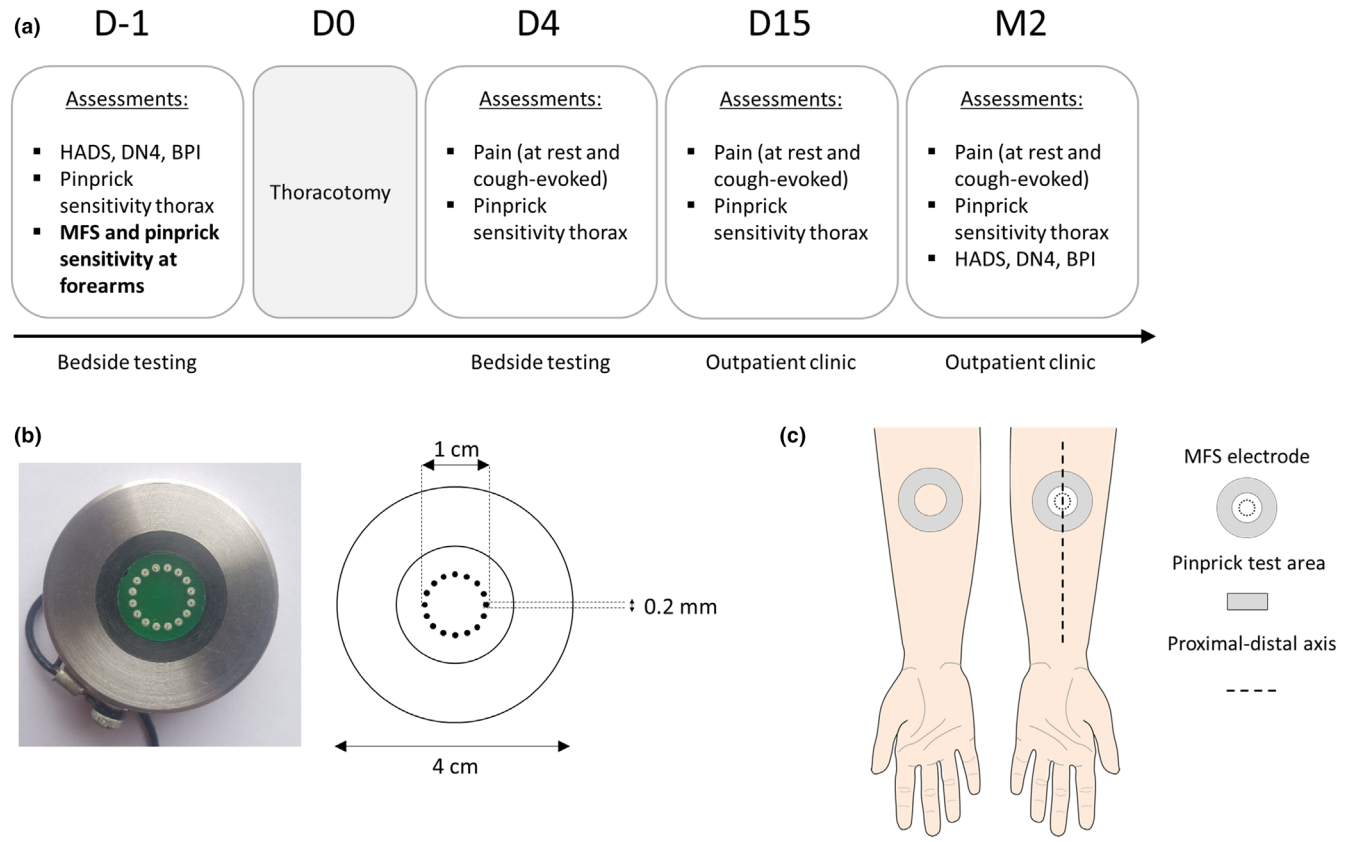

FIGURE 2 (a) Design of the study (see text). D-1 = day before surgery, D0 = day of surgery, D4 = Day 4 after surgery, D15 = Day 15 after surgery, M2 = 2 months after surgery. MFS = middle-frequency electrical stimulation to induce secondary hyperalgesia. HADS = Hospitality Anxiety and Depression Scale, DN4 = Douleur Neuropathique 4 Questions, BPI = brief pain inventory. (b) Characteristics of the MFS electrode. (c) MFS was applied through the MFS electrode. Changes in pinprick sensitivity were assessed before and after MFS within the grey areas. The length of the area of increased pinprick sensitivity was assessed along the proximal-distal axes at the arm that received MFS.

MFS was applied was counterbalanced according to the side of surgery. The electrical pulses were triggered by a digital–analogue interface (National Instruments, Austin, USA) controlled by MATLAB 2014B (The MathWorks Inc., Natick, USA) and delivered using a constant current electrical stimulator (Digitimer DS5, Digitimer, UK) via a specially designed electrode (Figure 2b). The electrode consists of 16 blunt stainless steel pins with a diameter of 0.2 mm protruding 1 mm from the base. The 16 pins are placed inside a circle with a diameter of 10 mm and serve as the cathode. A stainless-steel reference electrode that serves as the anode is concentrically located and has an inner diameter of 22 mm and an outer diameter of 40 mm. The intensity of MFS was individually adjusted to 20 times the detection threshold to a single non-charge-compensated monophasic pulse (pulse width: 2 ms). The detection threshold was determined using the method of limits. During the MFS stimulation, patients were instructed to rate each train on a Numeric Rating Scale (NRS) that ranged from 0 ('No pain') to 100 ('Maximum pain imaginable').

2.3.2 | Assessment of MFS-induced secondary hyperalgesia

The assessment of MFS-induced secondary hyperalgesia was performed as described in Cayrol et al. (2020), using a 128 mN calibrated mechanical pinprick stimulator (MRC Systems, 200 Heidelberg, Germany). Mechanical pinprick sensitivity was evaluated before and 30, 35 and 40 min after applying MFS. At each time-point, a total of three stimuli were applied to the forearm receiving MFS within a circle of 1.5 cm outside the cathode and to the homologous skin of the contralateral control arm (Figure 2c). The pinprick stimuli were delivered perpendicular to the skin and were never delivered twice at the exact same location, to avoid sensitizing the skin. After each pinprick stimulus patients were asked to rate the perceived intensity on a Numeric Rating Scale (NRS) ranging from 0 ('No detection') to 100 ('Maximal pain imaginable'), with 50 representing the transition from non-painful to painful domains of sensation. At all three post-MFS measurements, after collecting the perceived intensity ratings, we also estimated the length of the area of secondary hyperalgesia at the

MFS-stimulated arm along the proximal-distal axis of the volar forearm (Figure 2c). For this, we used the same pinprick stimulator to stimulate the skin along the proximal-distal axis originating from the centre of the area at which MFS was delivered. Mechanical pinprick stimulation started close to the cubital fossa and just before the wrist. Each stimulus was separated by steps of 1 cm, at a pace of 1-s stimulation and 1-s interval, in the direction of the MFS site (Cayrol et al., 2020). During the mapping, patients were instructed to keep their eyes closed and to say 'now' when they felt a clear increase of pinprick sensitivity. Then, the pinprick stimulation was delivered in steps of 0.5 cm before and after this point to confirm the border.

2.4 | Assessment of postsurgical pain

For evaluating the intensity of clinical postsurgical pain it is recommended to differentiate between pain at rest and movement-evoked pain (Gilron et al., 2024). At Day 4 (D4), Day 15 (D15) and 2 months (M2), patients were asked to evaluate their pain intensity at rest and during coughing as follows. First, they were asked to evaluate their pain at rest using a NRS ranging from 0 ('No pain') to 100 ('Maximal pain imaginable'). Then, they were instructed to couph while sitting upright, and to report the intensity of perceived pain using the same NRS.

2.5 | Thoracic surgery

Patients underwent a posterolateral thoracotomy (fifth to sixth intercostal space) for anatomical resection of lung cancer. All thoracotomies were limited, muscle-sparing (Serratus muscle) and performed by the same surgeon (VL).

2.6 | Anaesthesia and postoperative analgesic treatment

Patients were premeditated with alprazolam 0.5 mg or 1 mg. General anaesthesia was induced with sufentanil (max 0.2 mcg/kg), propofol (1–2 mg/kg), rocuronium or atracurium (0.5 mg/kg, adjusted, according to neuromuscular monitoring) and ketorolac (0.5 mg/kg and max 30 mg). General anaesthesia was maintained with a continuous administration of propofol or sevoflurane, titrated based on the intraoperative EEG. An epidural catheter was inserted before induction of general anaesthesia in all patients, unless contraindicated or technically impossible. Intraoperative analgesia was achieved with a levobupivacaine 0.5% and sufentanil bolus, followed by a continuous infusion or iterative boluses every 50 min (levobupivacaine 0.25%). Postoperative analgesia was provided by patient-controlled epidural analgesia (PCEA, levobupivacaine). Patients without epidural received intraoperative ketamine (0.5 mg/kg followed by 0.25 mg/kg/h) and postoperative patient-controlled intravenous analgesia (PCIA, morphine or piritramide).

2.7 | Assessment of mechanical pinprick sensitivity around the scar

At the day before surgery (D-1) the mechanical pinprick sensitivity of the skin of the side to be operated was assessed using the same mechanical pinprick stimulator as for the assessment of pinprick sensitivity before and after MFS. Patients were asked to lay on the non-operated side and a total of three pinprick stimuli were delivered in the region of the future surgical incision. After each stimulus, patients were asked to rate the perceived intensity on a NRS ranging from 0 ('No detection') to 100 ('Maximal pain imaginable'), with 50 representing the transition from non-painful to painful domains of sensation.

At Day 4 (D4), Day 15 (D15) and 2-month (M2) follow-up, mechanical pinprick sensitivity of the skin surrounding the scar was assessed using the same pinprick stimulator. First, the area of secondary hyperalgesia was determined. For this, pinprick stimulation was applied along 14 radial lines (see Supplementary Material). For each line, the stimulation started far outside the scar and was delivered in steps of 0.5 cm towards the scar until the patient reported a clear increase in pinprick sensitivity, which indicated the border and was marked on the skin. The distance between this point and the scar was measured and noted. The stimulation stopped approximately 0.5 cm before the scar.

Then, three pinprick stimuli were delivered inside the area of secondary hyperalgesia (at least 0.5 cm from the scar), or if not present, 1 cm around the scar. After each stimulus, patients were asked to rate the perceived intensity on the same NRS as the one used for assessing changes in pinprick sensitivity at the chest at the day before surgery (D-1).

The area size of secondary hyperalgesia was estimated using a cubic spline interpolation ('interpclosed' function using cubic pchip interpolation; Santiago Benito 2021 MATLAB) across all 14 points.

2.8 | Questionnaires

The Hospital Anxiety and Depression Scale (HADS) was designed to detect states of depression and anxiety

in the setting of a hospital or a medical outpatient clinic (Zigmond & Snaith, 1983). The scale consists of 14 items. Seven relate to anxiety and seven to depression. Each item is scored on a scale from 0 (absence of symptom) to 3 (maximum symptom severity).

The Douleur Neuropathique 4 questions (DN4) questionnaire was used to screen for a possible neuropathic pain. The DN4 consists of 10 questions assessing sensory descriptors and signs associated with neuropathic pain (Bouhassira et al., 2005). A score ≥4 is used as a cutoff for possible neuropathic pain.

The brief pain inventory (BPI) was used to evaluate the intensity of pain and its interference in daily activities. It was designed to assess the severity and impact of pain experienced primarily, but not exclusively, by cancer patients (Keller et al., 2004). It is divided into two parts: one part enquires about pain intensity (sensory dimension) and the other part about pain interference (reactive dimension). Items are scored on a 0–10 scale, where 0 indicates no pain or interference and 10 indicates the highest imaginable pain or complete interference (Keller et al., 2004).

2.9 | Statistical analysis

All statistical analyses were performed in JASP v. 17 (www.jasp-stats.org).

2.9.1 | Primary outcome

To answer the question of whether MFS-induced secondary hyperalgesia is associated the likelihood of having pain (yes or no) 2 months after surgery, we conducted two univariate logistic regression analyses for each of the variables separately (model 1: MFS-induced change in pinprick intensity; model 2: length of the MFS-induced area of secondary hyperalgesia) and a multivariate logistic regression analysis with both variables (model 3). The goodness-of-fit of each model was assessed using the chi-square statistic, associated *p*-value, the McFadden *R*-squared, considered a measure of 'predictive power' (Hughes et al., 2019) and the Akaike Information Criterion (AIC) which estimates the prediction error. The classification performance of the models was evaluated with the area under the Receiver Operating Characteristic (ROC) curve.

2.9.2 | Secondary outcomes

We calculated a Pearson correlation to investigate if there was a relationship between the length of the area of MFS-induced secondary hyperalgesia and the spatial extent of the area of incision-induced secondary hyperalgesia at D4 after surgery. The area of incision-induced secondary hyperalgesia was normalized to the length of the scar (which was different across patients) and expressed as its square root.

To assess if incision-induced secondary hyperalgesia at D4 is associated with pain at 2 months we conducted two univariate logistic regression analyses: one for the change in perceived intensity (model 1) and one for the extent of the area (model 2), and a multivariate analysis with both variables were included (model 3).

We also investigated whether the reported pain intensity at D4 is associated with the presence of pain at 2 months. For this, we ran two univariate logistic regression analyses: one with the pain at rest at D4 (model 1) and one with the cough-evoked pain at D4 (model 2), and a multivariate analysis where we included both variables in the same model (model 3).

3 | RESULTS

3.1 | Incidence of pain at 2 months (M2)

We found that eight patients (40%) reported pain at the 2-month follow-up. All these patients reported cough-evoked pain; two of them (10%) reported pain at rest (Figure 3). Since cough-evoked pain was more prevalent than pain at rest, we restricted our analysis to this type of pain at 2 months. Table 1 compares pre-, peri- and post-operative variables between patients with and without cough-evoked pain at 2 months.

3.2 | MFS-induced pain and secondary hyperalgesia

The mean (and SD) electrical detection threshold determined before applying MFS was 0.25 (±0.08) mA across all patients. The electrical detection threshold was not significantly different between the patients with and without cough-evoked pain at 2 months (Mann–Whitney *U* test: $U = 29.5$, $p = 0.162$). The median (and inter-quartile range) threshold was 0.26 (0.25–0.30) mA for the patients without pain and 0.20 (0.12–0.30) mA for the patients with pain.

Figure 4a shows the pain intensity elicited by MFS (averaged across the 12 trains) for both groups (with and without cough-evoked pain at 2 months). Figure 4b shows the pain intensity for each train. Figure 4c shows the increase (compared to baseline and control site) in perceived pinprick intensity induced by MFS. Figure 4d shows the length of the area of secondary hyperalgesia.

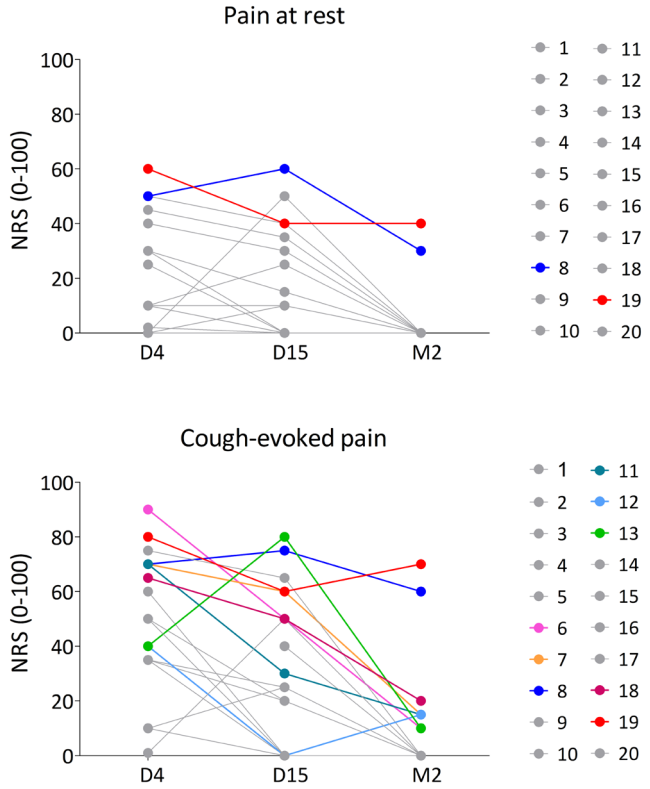

FIGURE 3 Pain scores for pain at rest (top) and during coughing (below) at D4, D15 and M2 for each patient (numbers on the right). Coloured lines are those patients reporting pain at the 2-month follow-up. NRS, Numeric Rating Scale.

3.3 | Primary outcome

First we inspected the data for outliers and multicollinearity. We found no values larger than 1 at the Cook's Distance test and no values larger than 3 for the Standardized Residuals. We found that the length of hyperalgesia and change in perceived intensity were correlated (Pearson's $r=0.605$, $p=0.005$), but less than 0.8 (critical threshold). The Variation Inflation Factor (VIF) was 1.173 (threshold for multicollinearity is at 4).

The logistic regression results are shown in Table 2. All three models were statistically significant, indicating that they all provide a significantly better fit to the data than a model without predictors. The McFadden R-squared is larger for models 2 and 3 compared to model 1, indicating that these models have more predictive power. According to the area under the ROC curve (AUC), models 1 and 2 performed excellently (AUC >0.8, Table 2) and model 3 outstandingly (AUC >0.9). The AIC of models 2 versus 3 were comparable (model 2: 18.95 and model 3: 20.48) using the criterion of a difference less than two points. However, the AIC of model 1 was larger (24.28) compared to model 3.

The univariate logistic regression analyses (models 1 and 2) revealed a significant positive coefficient for both the change in perceived intensity and the length of the area (Table 3). A positive coefficient means that an increase in the unit of the predictor is associated with an increase in the probability of having cough-evoked pain 2 months after surgery. For example, in model 2 the odds ratio (OR) is 2.070, meaning that for each additional centimetre there is a 107% increase in the odds of having cough-evoked pain at 2 months after surgery. In the multivariate analysis (model 3) however, neither predictor was statistically significant.

3.4 | Secondary outcomes

We found a significant and positive correlation ($r=0.533$, $p=0.019$) between the length of the area of MFS-induced secondary hyperalgesia and the spatial extent of the area of incision-induced secondary hyperalgesia at Day 4 normalized for scar length.

The logistic regression analysis with the incision-induced secondary hyperalgesia at Day 4 showed that the model with the change in perceived pinprick intensity (model 1) was not statistically significant (chi-squared = 1.299, $p=0.250$, McFadden R-squared = 0.048). In contrast, the model with the spatial extent (model 2) was statistically significant (chi-squared = 8.200, $p=0.004$, McFadden R-squared = 0.317). The spatial extent was a significant positive predictor (coefficient = 0.620, SE = 0.294, Wald = 4.456, $p=0.035$, OR = 1.859, 95% CI = 1.045–3.305). Also, model 3 (with both the change in perceived intensity and spatial extent) was statistically significant (chi-squared = 8.642, $p=0.013$, McFadden R-squared = 0.334). The AUC of model 2 (AUC = 0.864) and model 3 (AUC = 0.852) were comparable. The AIC of model 2 (21.66) and model 3 (23.22) were also comparable. Thus, model 3 did not perform better than model 2.

At Day 4, 14 patients (70%) reported pain at rest and 18 patients (90%) reported cough-evoked pain. Three logistic regression analyses were performed; one with pain at rest at D4 (model 1), one with cough-evoked pain at D4 (model 2) and one with pain at rest and cough-evoked pain together (model 3). All three models were statistically significant and performed well (Table S1). Furthermore, the AIC was comparable between model 1 (21.951) or model 2 (22.141) vs. model 3 (23.142). The two types of pain (at rest and cough-evoked) were significantly correlated (Pearson's $r=0.787$, $p<0.001$), but the VIF was 1.876. Table S2 shows the logistic regression coefficients.

4 | DISCUSSION

This study aimed to investigate whether the individual susceptibility to developing MFS-induced secondary

TABLE 1 Patient characteristics.

Time	Variables	Without pain at M2 ($n=12$)	With pain at M2 ($n=8$)	p
Preoperative	Gender (M:F)	7:5	5:3	ns
	Age (years)	69.5 (46.0–77.8)	66.0 (50.0–72.3)	ns
	BMI	25.1 (23.9–29.4)	24.0 (22.9–27.6)	ns
	Hypertension (n)	4 (33.3%)	4 (50.0%)	ns
	HADS-Anxiety scale	7.0 (5.0–11.0)	7.0 (4.5–10.5)	ns
	HADS-Depression scale	5.0 (4.0–6.8)	2.5 (2.0–5.8)	ns
	DN4 (n)[a]	0	0	–
	Pre-existing pain (n, %)	2[b] (16.7%)	3[c] (37.5%)	ns
	Pain at this moment[d] (n, %)	0 (0%)	3 (37.5%)	ns
	Pinprick thorax (NRS)	5.8 (2.3–10.9)	18.3 (4.3–27.8)	ns
Perioperative	Premedication (n, %)	4 (33.3%)	3 (37.5%)	ns
	Epidural (n, %)	9 (75%)	7 (87.5%)	ns
	Levobupivacaine (mg)	25 (20–25)	25 (25–25)	ns
	Sufentanil 10 μg (n, %)	4 (33.3%)	7 (87.5%)	ns
	Maintenance (mL)	12.5 (8.8–27.5)	12.5 (12.5–15.6)	ns
	Duration surgery (min)	141 (106–177)	148 (123–181)	ns
	Type of method (lob:bilob:wed:seg:lymp)[e]	7:1:2:2:0	3:1:1:1:2	ns
	Complications	4	0	ns
Postoperative				
D0-4	Mode of administration analgesia (PCIA:PCEA)[f]	4:7	1:7	ns
D4	Length of the scar (cm)	10.0 (9.1–13.4)	11.8 (9.8–12.8)	ns
	Pain—at rest (NRS)	2.0 (0.0–10.0)[g]	35.0 (13.8–50.0)	0.0071
	Pain—cough-evoked (NRS)	35.0 (10.0–50.0)[g]	70.0 (46.3–77.5)	0.0145
	Pinprick thorax (NRS)	11.7 (1.3–28.3)[g]	31.7 (11.3–49.2)	ns
	Normalized SH area (cm^2)	14.6 (0.4–39.1)[g]	46.1 (29.2–88.6)	0.0093
D15	Pain—at rest (NRS)	0.0 (0.0–21.3)	22.5 (10.0–40.0)	0.0388
	Pain—cough-evoked (NRS)	20.0 (0.0–36.3)	55.0 (35.0–71.3)	0.0187
	Pinprick thorax (NRS)	13.3 (3.3–33.3)[g]	20.0 (15.0–33.3)[h]	ns
	Normalized SH area (cm^2)	18.3 (12.3–52.5)[g]	36.9 (13.4–46.3)[h]	ns
M2	Pain—at rest (NRS)	0.0 (0.0–0.0)	0.0 (0.0–22.5)	–
	Pain—cough-evoked (NRS)	0.0 (0.0–0.0)	15.0 (11.3–50.0)	–
	Pinprick thorax (NRS)	3.3 (0.0–19.6)[i]	15.8 (10.4–27.1)	ns
	Normalized SH area (cm^2)	5.8 (0.0–31.5)[i]	23.7 (15.5–34.6)	ns
	HADS—Anxiety scale	5.5 (3.3–8.8)	1.5 (0.3–6.0)	ns
	HADS—Depression scale	4.0 (2.3–6.8)	3.0 (0.5–4.8)	ns
	DN4 (n)[a]	0	2	ns
	BPI-Mean Pain Severity	0.0 (0.0–0.2)	1.0 (0.0–2.1)	0.0452
	BPI-Interference	0.0 (0.0–0.0)	0.8 (0.0–2.3)	0.0293

Note: Number of patients (n) with percentages (%) or medians with interquartile ranges are shown. $p=p$-value from either a chi-squared test in the case of frequencies or a non-parametric Mann–Whitney U test. – = not possible to run the Mann-Witney U test because of all zeros in the without pain group. D0-4 = Day 0 to 4 after surgery, D4 = Day 4 after surgery, D15 = Day 15 after surgery, M2 = 2-month follow-up.

Abbreviations: BMI, body mass index; BPI, brief pain inventory; DN4, Doleur Neuropathique 4 Questions; HADS, Hospital Anxiety and Depression Scale; NRS, Numeric Rating Scale; ns, not significant.

[a]Number of patients that scored ≥4.

[b]One patient had low back pain and one patient had shoulder pain.

[c]One patient had low back pain, one patient had pain in the post-nephrectomy belt and one patient had shoulder pain (probably related to a previous thoracotomy).

[d]The number reported here refers to the number of patients reporting pain at that moment and was based on the item BPI-Now.

[e]Refers to Lobectomy: Bi-lobectomy: Wedge resection: Segmentectomy: Lymph node dissection.

[f]PCIA = Patient-Controlled Intravenous Analgesia, PCEA = Patient Controlled Epidural Analgesia.

[g]$N=11$.

[h]$N=7$.

[i]$N=8$.

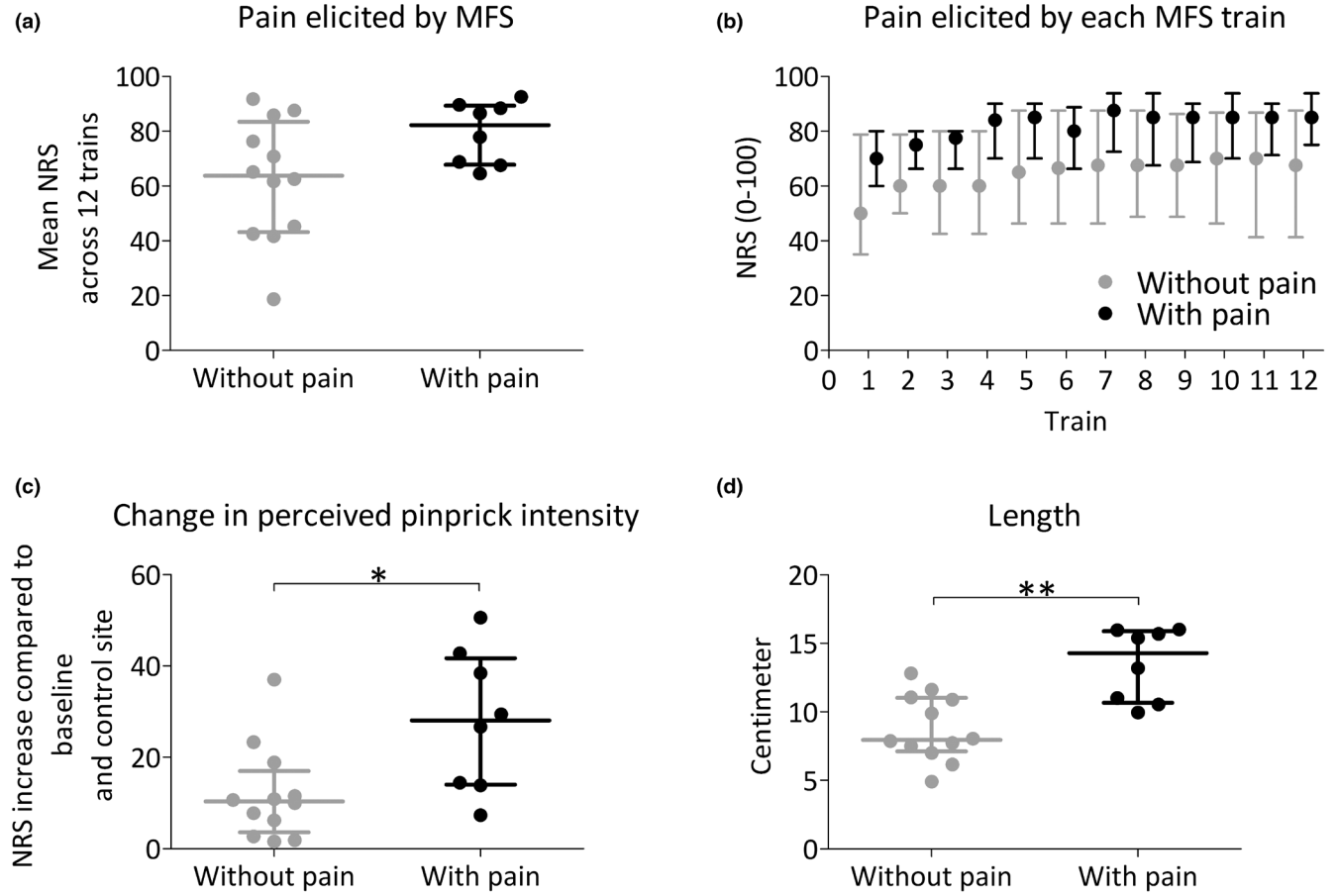

FIGURE 4 MFS-induced pain and secondary hyperalgesia compared between patients with and without cough-evoked pain at the 2-month follow-up. (a) Median pain elicited by MFS (averaged across all 12 trains). (b) Median pain induced by MFS for each train. (c) Median change in perceived pinprick intensity. (d) Median length of the area. Shown are the median and interquartile ranges. Each dot represents a single patient. *$p < 0.05$, **$p < 0.01$. Significance refers to the Mann–Whitney *U* test.

TABLE 2 Logistic regression model summary for cough-evoked pain 2 months after surgery.

Model	Factors	Chi-squared (df)	*p*-value	McFadden R^2	AUC
1	Change in perceived intensity	6.639 (18)	0.010	0.247	0.833
2	Length of the area	11.968 (18)	0.0005	0.445	0.885
3	Change in perceived intensity **AND** Length of the area	12.439 (17)	0.002	0.462	0.938

Note: For each model the chi-squared, its *p*-value, the McFadden R^2 and area under the receiver operating curve (AUC) are shown.

hyperalgesia preoperatively is associated with the presence of post-thoracotomy pain at 2 months. We found that 40% of the included patients reported cough-evoked pain at the 2-month follow-up. We show, for the first time, that the magnitude (intensity and extent) of preoperatively assessed MFS-induced secondary hyperalgesia displays excellent discriminative power (AUC >0.9) for the presence or absence of cough-evoked pain 2 months after thoracotomy. These results support the hypothesis that a heightened individual susceptibility to develop experimentally induced secondary hyperalgesia may identify patients who are vulnerable to the development of persistent post-thoracotomy pain.

4.1 | Electrically and incision-induced secondary hyperalgesia are correlated

Interestingly, the extent of the area of MFS-induced secondary hyperalgesia and the extent of the area of incision-induced secondary hyperalgesia were correlated. This has already been demonstrated with experimental

TABLE 3 Logistic regression coefficients for cough-evoked pain 2 months after surgery.

Model	Factors	Coefficient	Error	OR	95% CI	Wald	*p*-value
1	Change in perceived intensity	0.098	0.046	1.103	1.008–1.206	4.555	0.033
2	Length of the area	0.728	0.324	2.070	1.098–3.904	5.052	0.025
3	Change in perceived intensity **AND**	0.039	0.058	1.040	0.928–1.166	0.453	0.501
	Length of the area	0.612	0.342	1.843	0.943–3.602	3.202	0.074

Note: For each model, the regression coefficient with its error term, the odds ratio with the 95% confidence interval and the Wald statistic with its *p*-value are shown.

heat-induced secondary hyperalgesia and incision-induced secondary hyperalgesia after gynecologic surgery (Dirks et al., 2002). These findings suggest that the individual susceptibility for spreading hyperalgesia may be similar across different pain-inducing events.

4.2 | Mechanisms underlying electrically and incision-induced secondary hyperalgesia

In a recent study, Patel et al. (2024) recorded in rats, before and after HFS, the responses of spinal wide-dynamic range (WDR) neurons elicited by mechanical pinprick stimuli delivered to the glabrous skin of the paw. They found increased WDR neuron responses after HFS when the mechanical stimuli were applied to the HFS-treated area and the adjacent area. They also found that when HFS was applied to the receptive field, an expansion of receptive field size for mechanical pinprick stimuli was observed but when HFS was delivered adjacent to the receptive field, no expansion of the receptive field was observed. These findings suggest that the increased WDR neuron responses elicited by mechanical pinprick stimuli applied at distant sites might involve a mechanism different from the one underlying the receptive field expansion. A candidate mechanism could be descending facilitation (Patel et al., 2024; Pertovaara, 1998; Urban & Gebhart, 1999).

Similar effects can probably be observed after MFS and the question arises whether the variability in the area size of MFS-induced secondary hyperalgesia observed in patients the day before surgery could have been (partly) the result of individual differences in descending facilitation.

Similar findings with respect to WDR neuron activity have been observed after incision of the paw (Brennan et al., 1996; Vandermeulen & Brennan, 2000; Zahn & Brennan, 1999). On the other hand, a recent study analysing skin biopsies of human volunteers 24 h after skin incision revealed that the size of the area of hyperalgesia surrounding an incision is associated with a specific protein profile (Segelcke et al., 2023). While subjects with large areas of hyperalgesia showed a more inflammatory profile, subjects with a small area showed an anti-inflammatory profile. These results suggest a peripheral contribution to incision-induced hyperalgesia after thoracic surgery. Taken together, a posterolateral thoracotomy induces secondary hyperalgesia that probably results from both peripheral and central mechanisms.

4.3 | Incision-induced hyperalgesia and postoperative pain at D4 are associated with cough-evoked pain at 2 months

Given that the extent of the area of MFS-induced secondary hyperalgesia and the extent of the area of incision-induced secondary hyperalgesia were correlated in our patients, and that the extent of the area of MFS-induced secondary hyperalgesia was associated with cough-evoked pain at 2 months, it may not be surprising that the extent of postoperative hyperalgesia was also associated with cough-evoked pain at 2 months.

We also found that the reported pain intensity on Day 4 was associated with cough-evoked pain at 2 months. This is in line with the known literature, as the intensity of postoperative has long been recognized as a predictive factor for the development of persistent postsurgical pain in several surgical models, including thoracotomy (Lim et al., 2022). Besides postoperative pain, younger age, female sex, hypertension, preoperative pain, open thoracotomy, more extensive procedures (bilobectomy, pneumonectomy, lobectomy plus wedge resection and pleurectomy) and wound complications were also found to be predictors for persistent post-thoracotomy pain (Lim et al., 2022).

A previous study analysed pain trajectories up to 1 year after thoracic surgery and found three different groups (Liu et al., 2021, their fig. 2). One group reported (on average) mild pain after surgery that remained mild for 12 months. A second group reported moderate pain after surgery, which substantially reduced within 3 months after surgery to the point that the reported pain intensity

completely overlapped with group 1. Finally, group 3 also reported moderate pain after surgery, but this pain did not reduce throughout the year. The cough-evoked pain reported by the patients in the present study at the 2 months follow-up might represent the same trajectory as the second group described in the study of Liu et al. Indeed, cough-evoked pain seems to decrease in the majority of the patients between the 15-day follow-up measurement and the 2-month measurement. This could point to a healing process that may be related to ongoing nociception or inflammation.

Some studies also reported anxiety and depression as risk factors for post-thoracotomy pain (Lim et al., 2022). Indeed, a recent meta-analysis showed that state anxiety has a significant association with persistent postsurgical pain (Giusti et al., 2021). In our study we found no significant differences in the HADS-anxiety score or HADS-depression score between patients with and without cough-evoked pain. A likely possibility is that our sample size was too small to detect differences or that the way we tested for anxiety (HADS questionnaire) may not be sensitive enough.

4.4 | Limitations

The end-point of our study was at 2 months; therefore, we cannot speak about chronic postsurgical pain, which is defined in the International Classification of Diseases (ICD-11) as pain that is present for at least 3 months after the initiating event (Schug et al., 2019). Whether the cough-evoked pain reported by the patients at the 2-month follow-up would still be present at 3 months remains to be investigated.

Our study sample size is small. Due to the COVID pandemic and its impact on clinical activity and access to patients for clinical research, we were able to recruit fewer patients in this period (2020–2021) of the study. Moreover, during the last period of our study, other clinical studies recruited patients of the same population, which probably reduced the number of patients available for our study as well. Finally, a significant number of recruited patients ($N = 9$, 22%) did not tolerate the entire MFS procedure and, therefore, dropped out. To reduce the drop-out rate as a result of MFS, one might consider lowering the stimulation intensity or using the high-frequency stimulation (HFS) protocol, in which only five trains are delivered (van den Broeke et al., 2019) or both. To further reduce the discomfort patients may experience from MFS or HFS one could explore if similar results can be obtained when the electrical stimulation is applied, for example, 1 week before surgery instead of the day before.

The small sample size may have led to model overfitting and this hinders generalization. It also limited the number of predictors we could include in the regression models. In the literature, the rule of 10 events per variable is often advised (Ranganathan et al., 2017), although there seems to be no statistical justification for this recommendation (van Smeden et al., 2016). To conclude, for the sake of generalizability, our findings need to be replicated and validated in a larger independent cohort.

5 | CONCLUSION

Our findings indicate that the individual susceptibility to developing experimentally induced secondary hyperalgesia preoperatively may identify patients who are potentially vulnerable to the development of persistent post-thoracotomy pain. The ability to preoperatively identify patients at risk for developing persistent post-thoracotomy pain using a simple assessment of secondary hyperalgesia would be clinically helpful. It would allow targeted prevention measures that may reduce the incidence of persistent post-thoracotomy pain.

AUTHOR CONTRIBUTIONS

Conception and design: ENvdB, AM, CL, AS, PL, VL. Acquisition of data: ENvdB, SG, MC, CL. Analysis and interpretation of data: ENvdB, SG, CL. Writing of the manuscript: ENvdB, SG, MC, CL, AS, PL, AM, VL. Approved last version: ENvdB, SG, MC, CL, AS, PL, AM, VL. All authors discussed the results and commented on the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank all patients for their willingness to participate in the study.

FUNDING INFORMATION

ENvdB was supported by the Fonds de Recherche Clinique of UCLouvain (2018) and the ESA-BJA grant (BJA-ESAIC_GR_2020_EV). S.G. has received funding from the European Union's Horizon2020 Research and Innovation Program under grant agreement no 848068. This publication reflects only the authors' view, and the European Commission is not responsible for any use that may be made of the information it contains.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

ORCID

Emanuel N. van den Broeke https://orcid.org/0000-0002-6668-3217

REFERENCES

Bayman, E. O., & Brennan, T. J. (2014). Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: Meta-analysis. *The Journal of Pain*, *15*(9), 887–897. https://doi.org/10.1016/j.jpain.2014.06.005

Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., Cunin, G., Fermanian, J., Ginies, P., Grun-Overdyking, A., Jafari-Schluep, H., Lantéri-Minet, M., Laurent, B., Mick, G., Serrie, A., Valade, D., & Vicaut, E. (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*, *114*(1–2), 29–36. https://doi.org/10.1016/j.pain.2004.12.010

Brennan, T. J., & Kehlet, H. (2005). Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain: Not an easy path. *Anesthesiology*, *103*(4), 681–683. https://doi.org/10.1097/00000542-200510000-00004

Brennan, T. J., Vandermeulen, E. P., & Gebhart, G. F. (1996). Characterization of a rat model of incisional pain. *Pain*, *64*(3), 493–502. https://doi.org/10.1016/0304-3959(95)01441-1

Cayrol, T., Lebleu, J., Mouraux, A., Roussel, N., Pitance, L., & van den Broeke, E. N. (2020). Within- and between-session reliability of secondary hyperalgesia induced by electrical high-frequency stimulation. *European Journal of Pain*, *24*(8), 1585–1597. https://doi.org/10.1002/ejp.1613

De Kock, M., Lavand'homme, P., & Waterloos, H. (2001). 'Balanced analgesia' in the perioperative period: Is there a place for ketamine? *Pain*, *92*, 373–380. https://doi.org/10.1016/S0304-3959(01)00278-0

De Kock, M., Lavand'homme, P., & Waterloos, H. (2005). The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. *Anesthesia and Analgesia*, *101*, 566–572. https://doi.org/10.1213/01.ANE.0000157121.71808.04

Dirks, J., Møiniche, S., Hilsted, K. L., & Dahl, J. B. (2002). Mechanisms of postoperative pain: Clinical indications for a contribution of central neuronal sensitization. *Anesthesiology*, *97*(6), 1591–1596. https://doi.org/10.1097/00000542-200212000-00035

Gilron, I., Lao, N., Carley, M., Camiré, D., Kehlet, H., Brennan, T. J., & Erb, J. (2024). Movement-evoked pain versus pain at rest in postsurgical clinical trials and in meta-analyses: An updated systematic review. *Anesthesiology*, *140*(3), 442–449. https://doi.org/10.1097/ALN.0000000000004850

Giusti, E. M., Lacerenza, M., Manzoni, G. M., & Castelnuovo, G. (2021). Psychological and psychosocial predictors of chronic postsurgical pain: A systematic review and meta-analysis. *Pain*, *1*, 10–30. https://doi.org/10.1097/j.pain.0000000000001999

Hughes, G., Choudhury, R. A., & McRoberts, N. (2019). Summary measures of predictive power associated with logistic regression models of disease risk. *Phytopathology*, *109*(5), 712–715. https://doi.org/10.1094/PHYTO-09-18-0356-LE

Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., & Cleeland, C. S. (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *The Clinical Journal of Pain*, *20*(5), 309–318. https://doi.org/10.1097/00002508-200409000-00005

Lavand'homme, P., De Kock, M., & Waterloos, H. (2005). Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology*, *103*(4), 813–820. https://doi.org/10.1097/00000542-200510000-00020

Lim, J., Chen, D., McNicol, E., Sharma, L., Varaday, G., Sharma, A., Wilson, E., Wright-Yatsko, T., Yaeger, L., Gilron, I., Finnerup, N. B., & Haroutounian, S. (2022). Risk factors for persistent pain after breast and thoracic surgeries: A systematic literature review and meta-analysis. *Pain*, *163*(1), 3–20. https://doi.org/10.1097/j.pain.0000000000002301

Liu, C. W., Page, M. G., Weinrib, A., Wong, D., Huang, A., McRae, K., Fiorellino, J., Tamir, D., Kahn, M., Katznelson, R., Ladha, K., Abdallah, F., Cypel, M., Yasufuku, K., Chan, V., Parry, M., Khan, J., Katz, J., & Clarke, H. (2021). Predictors of one year chronic post-surgical pain trajectories following thoracic surgery. *Journal of Anesthesia*, *35*(4), 505–514. https://doi.org/10.1007/s00540-021-02943-7

Martinez, V., Ammar, S. B., Judet, T., Bouhassira, D., Chauvin, M., & Fletcher, D. (2012). Risk factors predictive of chronic postsurgical neuropathic pain: The value of the iliac crest bone harvest model. *Pain*, *153*(7), 1478–1483. https://doi.org/10.1016/j.pain.2012.04.004

Momeni, M., De Kock, M., Lavand'homme, P., Watremez, C., Van Dyck, M., & Baele, P. (2010). Abnormal sensations evoked over the chest and persistent peri-incisional chest pain after cardiac surgery. *Acta Anaesthesiologica Belgica*, *61*(2), 55–62.

Patel, R., Taylor, J. L., Dickenson, A. H., McMahon, S. B., & Bannister, K. (2024). A back-translational study of descending interactions with the induction of hyperalgesia by high-frequency electrical stimulation in rat and human. *Pain*, *165*(9), 1978–1989. https://doi.org/10.1097/j.pain.0000000000003166

Pertovaara, A. (1998). A neuronal correlate of secondary hyperalgesia in the rat spinal dorsal horn is submodality selective and facilitated by supraspinal influence. *Experimental Neurology*, *149*(1), 193–202. https://doi.org/10.1006/exnr.1997.6688

Quesada, C., Kostenko, A., Ho, I., Leone, C., Nochi, Z., Stouffs, A., Wittayer, M., Caspani, O., Brix Finnerup, N., Mouraux, A., Pickering, G., Tracey, I., Truini, A., Treede, R.-D., & Garcia-Larrea, L. (2021). Human surrogate models of central sensitization: A critical review and practical guide. *European Journal of Pain*, *25*(7), 1389–1428. https://doi.org/10.1002/ejp.1768

Ranganathan, P., Pramesh, C. S., & Aggarwal, R. (2017). Common pitfalls in statistical analysis: Logistic regression. *Perspectives in Clinical Research*, *8*(3), 148–151. https://doi.org/10.4103/picr.PICR_87_17

Salengros, J. C., Huybrechts, I., Ducart, A., Faraoni, D., Marsala, C., Barvais, L., Cappello, M., & Engelman, E. (2010). Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: Low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *Journal of Cardiothoracic and Vascular Anesthesia*, *24*(4), 608–616. https://doi.org/10.1053/j.jvca.2009.10.006

Schug, S. A., Lavand'homme, P., Barke, A., Korwisi, B., Rief, W., & Treede, R.-D. (2019). IASP taskforce for the classification of chronic pain. The IASP classification of chronic pain for ICD-11: Chronic postsurgical or posttraumatic pain. *Pain*, *160*(1), 45–52. https://doi.org/10.1097/j.pain.0000000000001413

Segelcke, D., van der Burgt, M., Kappert, C., Schmidt Garcia, D., Sondermann, J. R., Bigalke, S., Pradier, B., Gomez-Varela, D., Zahn, P. K., Schmidt, M., & Pogatzki-Zahn, E. M. (2023). Phenotype- and species-specific skin proteomic signatures for

incision-induced pain in humans and mice. *British Journal of Anaesthesia*, *130*(3), 331–342. https://doi.org/10.1016/j.bja.2022.10.040

Setälä, P., Kalliomäki, M. L., Järvelä, K., Huhtala, H., Sisto, T., & Puolakka, P. (2016). Postoperative hyperalgesia does not predict persistent post-sternotomy pain; observational study based on clinical examination. *Acta Anaesthesiologica Scandinavica*, *60*(4), 520–528. https://doi.org/10.1111/aas.12659

Urban, M. O., & Gebhart, G. F. (1999). Supraspinal contributions to hyperalgesia. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(14), 7687–7692. https://doi.org/10.1073/pnas.96.14.7687

van den Broeke, E. N., Gousset, S., Bouvy, J., Stouffs, A., Lebrun, L., van Neerven, S. G. A., & Mouraux, A. (2019). Heterosynaptic facilitation of mechanical nociceptive input is dependent on the frequency of conditioning stimulation. *Journal of Neurophysiology*, *122*(3), 994–1001. https://doi.org/10.1152/jn.00274.2019

van den Broeke, E. N., Lenoir, C., & Mouraux, A. (2016). Secondary hyperalgesia is mediated by heat-insensitive A-fibre nociceptors. *The Journal of Physiology*, *594*(22), 6767–6776. https://doi.org/10.1113/JP272599

van den Broeke, E. N., & Mouraux, A. (2014). High-frequency electrical stimulation of the human skin induces heterotopical mechanical hyperalgesia, heat hyperalgesia, and enhanced responses to nonnociceptive vibrotactile input. *Journal of Neurophysiology*, *111*(8), 1564–1573. https://doi.org/10.1152/jn.00651.2013

van Smeden, M., de Groot, J. A., Moons, K. G., Collins, G. S., Altman, D. G., Eijkemans, M. J., & Reitsma, J. B. (2016). No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. *BMC Medical Research Methodology*, *16*(1), 163. https://doi.org/10.1186/s12874-016-0267-3

Vandermeulen, E. P., & Brennan, T. J. (2000). Alterations in ascending dorsal horn neurons by a surgical incision in the rat foot. *Anesthesiology*, *93*(5), 1294–1302. https://doi.org/10.1097/00000542-200011000-00024

Yoon, S., Hong, W. P., Joo, H., Kim, H., Park, S., Bahk, J. H., & Lee, H. J. (2020). Long-term incidence of chronic postsurgical pain after thoracic surgery for lung cancer: A 10-year single-center retrospective study. *Regional Anesthesia and Pain Medicine*, *45*(5), 331–336. https://doi.org/10.1136/rapm-2020-101292

Zahn, P. K., & Brennan, T. J. (1999). Incision-induced changes in receptive field properties of rat dorsal horn neurons. *Anesthesiology*, *91*(3), 772–785. https://doi.org/10.1097/00000542-199909000-00030

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gousset, S., Cappe, M., Lenoir, C., Steyaert, A., Lavand'homme, P., Mouraux, A., Lacroix, V., & van den Broeke, E. N. (2025). Preoperative susceptibility to developing secondary hyperalgesia is associated with post-thoracotomy pain at 2 months. *European Journal of Pain*, *29*, e4768. https://doi.org/10.1002/ejp.4768